JANUARY 1952

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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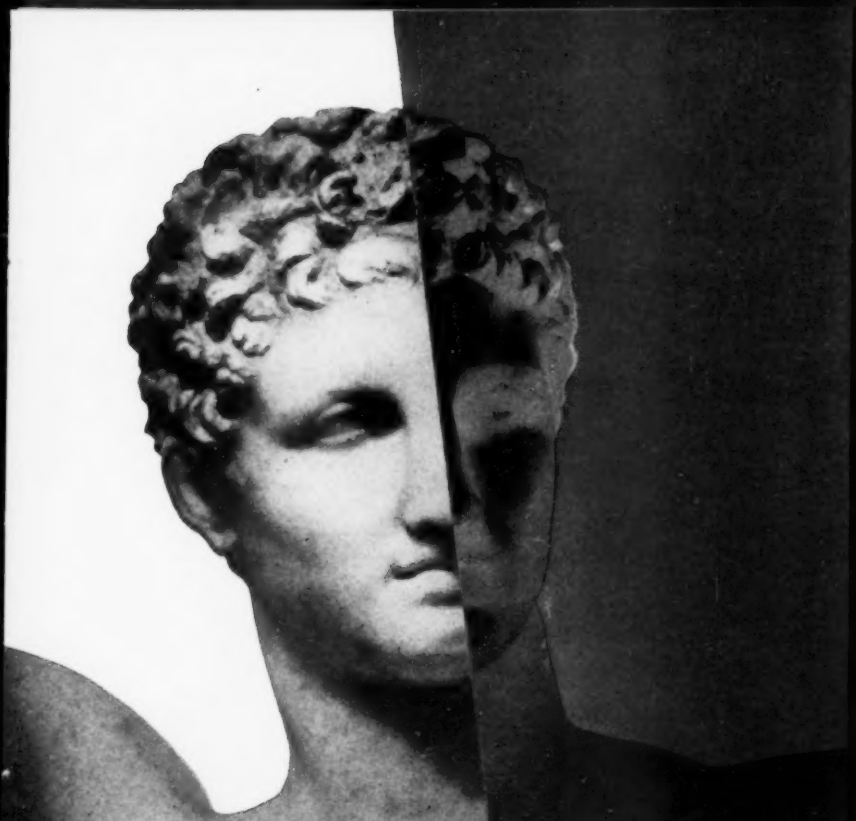

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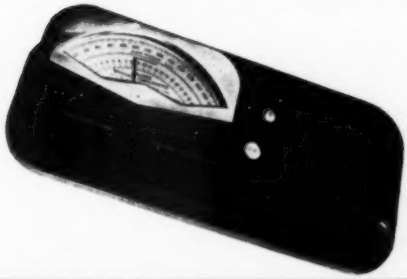

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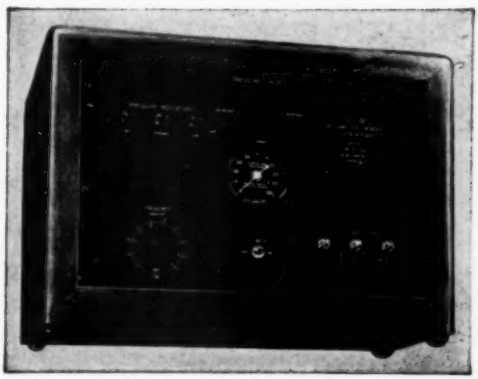

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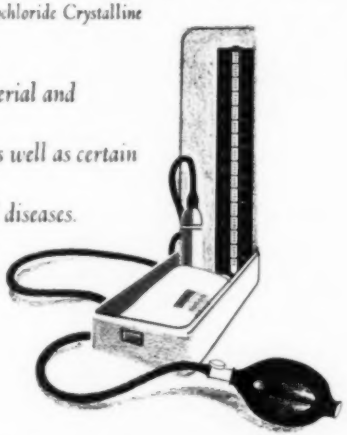

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 28, NO. 1 JANUARY 1952

CONTRACTION IN THE HEART MUSCLE FIBRE*

A. SZENT-GYÖRGYI

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MUSCLE has two functions: it shortens and creates tension. The two functions are, in their essence, but one, because one and the same change will produce contraction or tension according to conditions. If the ends of the system are free, it shortens. If they are fixed, they develop tension. Tension means that the contraction would occur with a certain force.

In order to create a system which could do all this Nature had to solve a number of problems of molecular engineering which we will discuss in succession.

In order to build a system which can shorten, Nature had to use thin and long protein particles. Thin and long particles always tend to fold up, thus shorten, especially if they are very small and are exposed to the bombardment of water molecules moved by heat-agitation. The thread-like, very thin and long protein particles, out of which Nature has built the contractile matter, is "myosin."

* Presented at the 24th Graduate Fortnight of The New York Academy of Medicine, October 10, 1951.

If the myosin particle tends to fold up anyway then the first question we have to answer is not how it shortens but what keeps it straight in resting muscle. There must be repulsive forces which repel, so to say, one end of the particle from the other. Such repulsive forces are always electric coulombic charges. The myosin molecule generates its charges by dissociation. Like other proteins, it has dissociating acidic COOH, and alkaline groups. On dissociation the acidic groups acquire a negative, the alkaline groups a positive charge. The number of acidic groups is slightly greater than that of the alkaline ones and consequently the myosin molecule has a negative net-charge.

This negative net-charge repels other equally charged protein particles. Looking, however, closer into these relations we find that it is not this net negative charge which keeps other particles away. The negative charges are balanced by positive K+ ions which surround the particle. They would actually remain in the closest proximity to the negatively charged particle, would heat-agitation not drive them away, as a wind whirls up dust. It cannot drive them away altogether because this is not permitted by the electric attraction. The end-result is that the myosin particle is surrounded by a cloud of positive K+ ions, thus a positively charged atmosphere, and if another myosin particle approaches it will be these positively charged atmospheres which meet first and repel one another, and thus keep the myosin in solution. This atmosphere will also have the tendency to expand because the positive ions in it repel one another. The end result will be that not only other particles are kept away but the particles will be kept straight, extended.

How strongly this positive ionic atmosphere will repel other similar structures depends chiefly on two factors. First: the number of charges. The number of positive charges in this atmosphere is equal to the number of the net negative charges of the particle itself. Second: the thickness of this positive ionic layer. If the K-ions get very close to the particle then this latter's negative charges neutralize this outward effect. The ionic atmosphere will still be there and keep the particle straight but will not repel other particles any more, which now can approach the myosin particle. Colloidal particles always tend to approach and stick together owing to the Van der Waals cohesive forces and so, if coulombic repulsions do not drive them apart, they approach, stick together, and the final result is the formation of flocculi which rapidly settle to the bottom, i.e., precipitate.

I am not losing my way in intricacies of colloidal chemistry. These problems are most important for the contraction of the muscle fiber, be it heart or body muscle. This will be evident if we discuss the second problem of molecular engineering Nature had to solve when creating the muscle. In resting muscle the myosin particle had to be kept straight and we have seen how this is done. The next problem is, how this particle can be made to contract not at a moment's but at a thousandth's second's notice. How can all these charges be taken away within sigmas? There is one method known to all of you by which a protein can be discharged, that is precipitated (since precipitation is the expression of such discharge), and this is: by adding another specifically built protein, a precipitin. Nature keeps in muscle such a precipitin for myosin. This protein has been discovered in my laboratory and is called actin. If an actin and a myosin particle meet in presence of a physiological salt-concentration they unite to a complex, actomyosin which becomes partly discharged. This discharge is a very involved process and the ions of the solution are involved in the reaction too. Here we are interested only in the end-result. The trick, applied thus by Nature, by which it produces the sudden folding of the myosin particle at a sigma's notice is thus to keep another protein, actin, at its side. The two proteins, in resting muscle, are separated by those repulsive forces we discussed before. The repulsive and attractive forces are carefully balanced, so to say, at the razor's edge. This balance is disturbed by the wave of depolarization which travels along the membrane and is called by physiologists "excitation." As a consequence of this disturbance actin and myosin get together and interact.

The next problem which had to be solved concerns energy-relations: how to make these into a powerful machine. If our muscle lifts a weight it does work. If a system does outside work it has to lose an equivalent amount of energy itself: its free-energy content decreases. If a great amount of work has to be done, as is the case in muscle, the system must lose a great amount of free energy. There must be thus a great difference in the energy-content of the two states of actomyosin, the uncontracted, resting, high-energy state and the contracted low-energy state. Myosin itself, together with actin, is unable to produce two such states with such a great difference in energy-content. Accordingly the contraction of which actomyosin is capable is very poor, the discharge very incomplete. Here comes ATP into the picture, that amazing sub-

stance which is in the center of cell-life and its energy changes. Muscle contains ATP (adenosine-triphosphate) in relatively high concentration. It is linked to the myosin by adsorption. It is actually not myosin which unites with actin, but a myosin-ATP complex. If this complex unites with actin to actomyosin-ATP we get a new substance which has two possible states, which differ greatly in energy content and physical appearance. The one state is similar to the ATP-free actomyosin, with straight and highly charged particles while in the other state the particles are completely discharged, maximally folded. This state contains much less free energy. Every physical system tends to go into the state in which it contains the least energy, so if this actomyosin-ATP is formed in muscle under the influence of excitation it spontaneously goes over into its energy-poor contracted state. The loss of energy can be used to lift a weight, do work or develop tension.

Now comes the last engineering problem which concerns relaxation, the return of the system into its original resting state.

The first law of thermodynamics tells us that in relation to energy, we cannot get something for nothing. So if the muscle has done work, has spent free energy in its contraction, it cannot return to its high-energy resting state without paying for the expense, that is to say, without liberating an equivalent amount of chemical, bound energy. This problem is solved by Nature by smuggling, so to say, energy into the ATP molecule. When the ATP molecule is constructed and its phosphate groups are linked together energy has to be invested to establish such links. This energy is released again when the link is split. The myosin has the ability to split this link, act as ATP-ase and release the chemical bound energy which puts the energy-balance right, makes debit and credit side of the account tally again.

From the point of view of muscular contraction the metabolic apparatus is nothing but a factory for ATP or more precisely a factory of high-energy-phosphate-bonds. The metabolic apparatus releases the energy of food stuffs and makes out of it ATP or some other form of high-energy-phosphate to replace by it the high-energy-phosphate links split in muscular contraction.

You have certainly noticed I mentioned ions at every turn. They play an important role in all happenings. It is the intracellular ionic atmosphere which decides the charges, the balance of repulsive and attractive forces, equilibrium-distances, the trend of actin and myosin

to part or to get together and, last but not least, decides also the tension developed in contraction, the development of tension being also intimately connected with the distribution of charges, is governed by ions. It follows without saying that the regulation of the intracellular ionic atmosphere is one of the most important points in cell-life. At the same time it is one of the most difficult problems. What makes it so difficult is the fact that this atmosphere cannot be kept constant for it changes when the fiber is working. Every contraction, thus every heart beat, disturbs it. At rest there is a high K-concentration and a low Na concentration inside the fiber. Here, inside the fiber, the K-ions are linked to the protein by electrostatic attractions. The membrane itself is impermeable to Na. When the wave of excitement depolarizes the membrane, the membrane becomes permeable to all ions and at the same time the charge-system of actomyosin collapses, which causes the K-ions to become entirely free. They can now diffuse away through the depolarized membrane according to the gradient of their concentration and the cell loses potassium. In the next instant, however, the membrane is recharged but meanwhile the fiber has lost K and we have a new ionic balance inside with less K. It takes time until the original balance is reestablished. The next contraction, if it follows soon, finds thus a changed ionic balance. The cell is thus faced with the problem how to build its actomyosin: should this actomyosin be constructed in such a way as to be capable of exerting its maximal tension at the resting ionic balance or at the balance which is found immediately after contraction. The heart has to work with permanent rhythmicity: beat follows beat. The ionic balance depends thus on the time-interval which elapsed since the preceding one, that is it depends on the frequency. It is natural then, that the actomyosin should be built in such a way that it works well at the ionic balance which is found soon after a beat and should work poorly at the balance which will be found after a longer pause.

These relations are beautifully demonstrated by a phenomenon discovered eighty years ago by an American physiologist, Baudich. Baudich, working on the isolated frog heart, found that if the heart is arrested for some time, say for a few seconds, the first beat after this pause is weaker than the last one preceding it. If a second beat was made to follow soon it was somewhat stronger. The heart thus gradually regained its strength. The gradual increase of the height of contraction was summed up by Baudich under the name of "staircase."

We can now interpret this phenomenon and say that a beat leaves a decreased K-ion concentration behind which favors contraction. If a longer pause occurs this favorable condition deteriorates. The heart accumulates too much potassium and the beat following the longer pause finds an unfavorable ionic balance and needs a number of beats following one another in more rapid succession to re-establish the favorable charge-distribution again.

Dr. Hajdu and myself studied this phenomenon some time ago. We could fully corroborate Baudich but also found that if we replace the Ringer solution in our cannula by serum, we could stop the heart for a longer period and the next beat after this pause was just as good as the last before it. There was no staircase or only a very mild one. We were thus able to conclude that serum contains a substance which eliminates the staircase and renders the membrane relatively impermeable to the potassium thrown out during contraction, and enabled the heart to maintain the favorable condition, following contraction, for a longer period. As chemists, naturally, we wondered what this substance in serum could be. We found it to belong to the sterols. Desoxycosterone had such an action which seemed to have a high degree of specificity. Of the number of sterols tested only the closely related progesterone had a similar action, as was found in experiments in which Dr. Oscar Hechter from the Worcester Institute for Experimental Biology came to our help. We found only one other group of substances which had a similar action and this was the closely related group of digitalis. Digitoxin and all the related heart glycosides produced such an action. These substances are one of the best friends of man, which come to his help when his heart begins to fail. This indicated that the staircase has far-reaching pathological importance. When the heart is damaged it seems to be unable to keep the potassium out. Whether the heart lacks the regulating sterols which help to keep the K out or is merely unable to bind these sterols, we do not know. What we know is that we can come to its help with digitalis which keeps the ionic balance right.

When a heart becomes insufficient the pulse rate goes up. This is probably the only way in which the heart can maintain a favorable K-balance. If it would beat more slowly the pauses would be too long for the damaged permeability and, similarly to the Baudich experiment the beats would become poorer and poorer and a vicious circle would be established. The only way out is to beat fast, let one beat follow the

other in order to keep the intracellular [K] at the lower level. However, by doing so the heart finds itself, if I may say so, between the devil and the deep blue sea: by reducing the period of rest it has less time for recovery, while by extending it it develops a downgrade staircase. It is here that the balance is put right by digitalis, which allows the heart to beat slowly without losing its strength. This is probably why one of the first symptoms of a digitalis therapy is the slowing of the heart rate.

What happens in many pathological processes seems to be analogous to what we see in the perfused frog heart: the freshly isolated frog heart is well provided with the regulatory substances and develops a high tension at all frequencies. At the point at which its membrane loses its regulatory substances the staircase develops and we have to increase the frequency gradually to maintain maximal tension. Eventually the heart fails, having no time for recovery. We can now put things right by digitalis which replaces the normal regulatory substances and allows the heart to beat *slowly* and *strongly* again. Concomitant with this change there is also a change in the whole form of the heart beat. If we register it on the smoked drum, we see that the diastole develops more slowly, the descending slope of the curve becomes flatter. This indicates that actin and myosin part less readily, have a tendency to get and stay together, the ionic balance having been changed in such a way as to increase the mutual attraction between the two proteins. If this effect is exaggerated by an excessive dose of digitalis, actin and myosin will be unable to part at all and contracture develops.

To conclude, let us sum up events once more in their natural sequence. There is no essential difference between heart and body muscle as far as the mechanism of contraction itself is concerned. There is, however, an essential difference in the mode in which the excitation is generated. In the body muscle excitation is produced in the nerve-ending by messages coming from the central nervous system. The heart muscle has no such innervation and has to generate its excitation itself. This excitation, that is the depolarization of the membrane is generated at a preferential point close to the sinus, but every point is capable to do the same only at a slower rate so that the pace, under normal conditions, is dictated by the sinus node. The membrane is built in such a way that the depolarization generated here becomes self-propagatory and runs through the whole length of the fiber membrane. In its wake the distribution of charges is disturbed and brings actin and myosin together.

How the depolarization actually does this we do not know. Z. Bay and myself showed that the wave of depolarization produces an electric field inside the fiber, parallel to its axis, but we were unable to show yet conclusively that it is this "window field," which transmits the excitation of the membrane to actomyosin. The membrane, however, not only produces, propagates and transmits excitation: at the same time it also regulates by its specific permeability the intracellular ionic atmosphere which decides the whole issue. Once actin and myosin united they contract with the aid of ATP, which by its splitting and rephosphorylation causes muscle to relax. If the membrane is repolarised, ATP rephosphorylated, we have the same condition as we had in resting muscle and actomyosin dissociates into actin and myosin. The latter stretches out and the muscle is at rest again; everything is set for a new contraction. At the side of this machinery is the metabolic apparatus which replaces the split high-energy-phosphate-bonds.

In the analyses of a pathological condition the first question, which has to be answered is, which part of this complex machinery is out of order? This question has not been answered yet for most diseases of muscle tissue. The reason is evident. Our ignorance of muscle is still very dense and we do not know the single processes involved in contraction, sufficiently yet. So, for instance, we have practically no notion of the chemical mechanism of excitation, we only know that ATP here too plays a central role. With the discovery of actin and actomyosin and its amazing reactions with ATP a solid basis is created for the study of these problems which represent one of the newest and almost virgin fields of scientific inquiry.

LIPID METABOLISM AND ATHEROSCLEROSIS*

The Ludwig Kast Lecture

AARON KELLNER

Director of Central Laboratories and Assistant Professor of Pathology, The New York Hospital-Cornell Medical Center

ARTERIOSCLEROSIS has until quite recently been regarded in the same frame of reference as the phenomena of aging, the implicit assumption being made that just as all living creatures pass inevitably from a period of growth and maturation into one of senility and decay, so too the vascular channels harden and wear out.[1] Hence, the degenerative changes in blood vessels came to be looked upon as the natural and inexorable sequelae of life, the price that human tissue paid for prolonged survival. Indeed, the acceptance of arteriosclerosis as a natural process, susceptible to neither remedy nor prophylactic, was for many years responsible for retarding fruitful investigations into its etiology and pathogenesis. It was not until the third and fourth decades of the present century that it became increasingly plain from clinical, morphological, and experimental observations that arteriosclerosis constituted more than a single morbid process, and furthermore, that its most serious manifestations were not essential concomitants of aging[1, 2] but represented rather an acquired abnormality, in Aschoff's words, a disease process "superadded to the process of aging."[3] This change in concept was an important one, for it came at a time when the infectious diseases had in large part been mastered and when diseases of the heart and blood vessels were becoming foremost among the afflictions of mankind; and it was soon to have a stimulating influence on thought and experiment in the field of vascular disease.

NOSOLOGICAL AND MORPHOLOGICAL CONSIDERATIONS

The imperfections of nomenclature have often proved a source of

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confusion and irritation in medicine, and to this the term arteriosclerosis is no exception. Coined by Lobstein in 1833, it is a generic term applied to a group of vascular diseases characterized morphologically by hardening of the vessel wall, and includes such heterogeneous conditions as atherosclerosis, Mönckeberg's or medial sclerosis, arteriolosclerosis, and the age-changes that do occur in blood vessels. In addition to embracing a diversity of clinical and pathological states, the term arteriosclerosis lays undue emphasis upon the hardening aspect, a feature that is scarcely an adequate criterion for estimating the severity of change within the artery wall, for hardening per se is a relatively benign process which produces little if any interference with the flow of blood. Thus, for example, Mönckeberg's sclerosis which leads to widespread and often confluent calcification of the media, particularly in the extremities, rarely impinges upon the calibre of the lumen unless it is complicated by other processes. Likewise, the changes that occur with age in the walls of blood vessels (and blood vessels like other tissues are susceptible in some measure to the ravages of time) consist primarily of loss of elasticity with resultant dilation and tortuosity,[4, 5] a phenomenon that is plain for all to see in the corkscrew temporal arteries exhibited by many individuals past the age of forty, and one that does not compromise the lumen or embarrass the flow of blood. Atherosclerosis, on the other hand, is vastly more serious, for it is characterized not so much by hardening of the vessel wall as by narrowing or obliteration of the lumen. This is an occlusive disease that affects the nutrient vessels of the heart or brain or kidney, and by progressively choking off the flow of blood, leads to functional alteration and, all too commonly, to disability and death. It is with atherosclerosis that we will be concerned in the ensuing presentation.

In the absence of more precise knowledge of its etiology and pathogenesis, atherosclerosis is for the present best defined in morphological terms, its distinctive and fundamental feature being the presence of stainable lipid within the lesion. The earliest recognizable lesions of atherosclerosis, of which the fatty flecks or streaks commonly present in the aorta even in childhood are a typical example, are made up of small focal collections of lipid, sometimes free though usually in foamy macrophages, just beneath the endothelium. These minute intimal cushions project only slightly into the lumen, and offer little or no hindrance to the flow of blood; indeed, they may at this stage even be

reversible. It is noteworthy that the endothelium overlying the area of initial involvement is almost always structurally intact – a fact that speaks strongly against the hypothesis that injury to the intima is the primary pathogenetic event. As the process continues, the lesions increase progressively in size and number and often coalesce to form large lipid-rich intimal plaques that gradually begin to encroach upon the lumen. With expansion of the lesions the foam cells in their depths undergo necrosis and disintegrate, discharging their lipid and cellular debris to convert the central portion into a soft, pultaceous mass – the atheroma from which the entire process derives its name. In time, secondary changes become manifest, prominent among which are thickening of the overlying endothelium, disruption of the elastica with invasion of the media, fibrosis, hyalinization, and calcification. Continued enlargement of the lesions leads eventually to serious diminution in the calibre of the lumen, especially in the relatively narrow vessels of the heart and brain, and slowly throttles the flow of blood through these vital channels. Not infrequently, the flow of blood in atherosclerotic vessels, particularly in the coronary arteries, may be halted more abruptly by thrombosis or by hemorrhage into an atheromatous area. These latter events, however, dramatic and lethal though they be, are but complications in the evolution of atherosclerosis. It is to the early and basic lesion – the infiltration of lipids into the intima – that we must turn for clues to the secrets of this morbid process.

Biological and Historical Considerations

Before examining the factors currently thought to be implicated in the causation of atherosclerosis, it would be useful in attaining perspective to touch briefly upon some features of the natural history of this disease. One biological aspect of atherosclerosis that deserves more consideration than it usually receives is the remarkable fact that man is the only mammal in which the disease occurs regularly to any significant degree. To be sure, wild animals in their natural habitat seldom live to old age and consequently might not be expected to manifest extensive atherosclerosis. Many animals, however, have been permitted to live their full life span in scientific laboratories and zoological gardens; furthermore, a great many of them have been carefully examined post mortem, one of the noteworthy studies in this connection being the 10,000 autopsies performed in the Philadelphia Zoo.[6] Analysis of this

post-mortem data by Herbert Fox reveals that while medial calcification is frequently encountered in the arteries of various mammals, the lesions of atherosclerosis are exceedingly rare; indeed, clinically significant atherosclerosis is virtually absent. Birds, on the other hand, not infrequently do exhibit considerable atherosclerosis, although the lesions are seldom of sufficient severity to produce symptoms or to cause death. This paucity of significant naturally-occurring atherosclerosis among animals stands in striking contrast to the extraordinary incidence of the disease in man, and provides a challenge for incisive thought and experiment to bring to light the metabolic or perhaps environmental factors that may be involved.

Since atherosclerosis as a serious and fatal disease appears to be limited to the human species, the question then arises whether it is a relatively new disease attacking man in our modern society or whether it has been an affliction of mankind from the days of antiquity. In the case of most diseases the answer to such a question would hinge upon the interpretation of a reference in Scripture or ancient legend; in the case of atherosclerosis, however, a clear answer is provided in one of the most intriguing chapters in the history of medicine. Some 40 years ago archeologists working in the valley of the Nile unearthed hundreds of mummies dating back more than 1500 years before the Christian era, and many of these were in such an excellent state of preservation, due to the favorable influences of a dry climate and the embalming procedures practised by the ancient Egyptians, that it was possible to remove portions of the aorta and other major vessels and to prepare remarkably good histological sections from them. Extensive studies of the arterial lesions of Egyptian mummies by Ruffer[7] and by Shattock[8] make it plain that atherosclerosis was a very common disease 3,000 and more years ago and that the morphological character of the lesions, their distribution, and severity differed in no way from those seen post mortem today. Man, it appears, has been a victim of atherosclerosis for thousands of years; and if, as some think, the anxieties and tensions of modern life contribute heavily to the causation of atherosclerosis, it would seem that the builders of the pyramids were in their time as much a prey to anxieties and tensions as are the splitters of the atom today.[9]

It is relevant to inquire whether such factors as race, age, or sex influence man's susceptibility to atherosclerosis. The question of racial

differences cannot be answered definitely at the present time. Atherosclerosis is said to be a relatively mild and infrequent disease amongst certain oriental peoples, the Chinese and Okinawans for example, and attempts have been made to correlate the observation with hereditary or dietary factors, the low consumption of fat and cholesterol-containing foods among those peoples being the distinction most often stressed.[10, 11] The data, however, must be scrutinized with care, since vital statistics in those countries are incomplete and not entirely reliable, and also, since the average life expectancy in those lands is so much shorter than it is in Western countries that figures for the incidence of diseases such as atherosclerosis and cancer, which require many years for their full development, are not really comparable. The evidence, therefore, for the existence of important racial differences must be regarded for the moment as not completely convincing. The role of heredity, on the other hand, has been well substantiated. For the extensive family studies of Wilkinson[12] and of Adlersberg[13] have demonstrated the existence of fairly common genetically transmitted abnormalities of lipid metabolism that are associated with the frequent and early development of clinical atherosclerosis; and conversely, it is well known that there are families that are singularly long-lived and relatively free from the disease.

The part played by age in the genesis of atherosclerosis has been much discussed. It is now generally agreed that though atherosclerosis is not a necessary result of "the wear and tear of life," it is indirectly related to the aging process in the sense that it is a cumulative and slowly progressive disease that becomes increasingly manifest with the passage of time. The lesions of atherosclerosis are frequently encountered early in childhood and, as a rule, their extent and severity become more prominent with advancing age. Though virtually no one is completely free from the mark of the disease, it is, nevertheless, striking to observe on occasion how slight may be the degree of atherosclerosis even in extremely aged individuals. The almost universal prevalence of the disease, coupled with the fact that advanced calcified and eroded lesions are regularly encountered in association with fresh, soft, lipid-rich lesions has led to the concept of atherosclerosis as an episodic disease.[14] Thus, at irregular intervals throughout life, if the proper conditions are present (and they appear to be present to some extent in most of us), clusters of lesions are formed which then slowly undergo degenerative or perhaps even some retrogressive changes, to be followed at some

future date by a repetition of the cycle, so that at the end of life there is revealed to the pathologist's eye as an end result the sum total of these additive insults to the vascular tree.

When compared with the male, the female of the human species leads a charmed life with respect to atherosclerosis. Serious coronary artery disease, for example, is remarkably rare in females under age 40, though it is not at all uncommon in the young male, and the decreased susceptibility of the female to the disease is maintained consistently even in the later decades of life, but to a somewhat lesser degree. This freedom from atherosclerosis enjoyed by females is, of course, only a relative one, for they do develop atheromata that are identical in morphology and location to those seen in the male, but at each age level the severity of the lesions in the female, as well as the clinical consequences thereof, are distinctly less marked.[15] It is only when they suffer from diabetes or hypertension that females manifest a degree of atherosclerosis comparable to that of the male. It may be noted, parenthetically, that the advantage possessed by the "weaker" sex with regard to atherosclerosis is in large measure responsible for the fact that as a group they can look forward to decidedly greater longevity than males.

Lipids in Atherosclerosis

The concept that atherosclerosis is fundamentally a disorder of lipid metabolism derives from several sources: first, the demonstration by morphological and chemical means that the lesions themselves contain abundant lipid; second, the oft-made clinical observation that disease states characterized by abnormally high blood lipids are frequently associated with premature atherosclerosis; and third, and perhaps most important, the production of atherosclerosis in animals by experimental procedures that disturb their lipid balance.

It was appreciated by Virchow almost a century ago on morphological grounds that lipids are a prominent constituent of atheromatous plaques.[16] More precise chemical studies by Windaus,[17] Schönheimer,[18] and others[19, 20] have since shown that the lesions of atherosclerosis are rich in cholesterol and cholesterol esters, while containing in addition an admixture of other lipids, notably phospholipids and neutral fat. Indeed, the lipid composition of early atheromatous plaques is so similar to that of blood plasma as to suggest that the atheromatous

lipids are in fact derived from the plasma. There was, however, no direct confirmation of this view until quite recently, when it was demonstrated that radioactive cholesterol administered to animals can be detected in the atheromatous foci,[21] and further, by studies which show that under normal conditions the endothelium is permeable to a considerable portion of the plasma lipids.[22] The concept that plasma lipids stream through the endothelium and, under certain conditions to be discussed presently, leave behind a fatty sludge is a basic one in present-day understanding of the pathogenesis of atherosclerosis, and has been aptly and colorfully termed the "delta theory."[23]

Clinicians have long sensed that there is some causal connection between lipid metabolism and atherosclerosis because of the frequent observation that patients with diabetes, xanthomatosis, hypothyroidism, and nephrosis, who exhibit marked hypercholesterolemia, are prone to develop severe atherosclerosis and often at a relatively early age. Moreover, study of selected groups of patients with coronary occlusion and myocardial infarction reveal that in general they have blood cholesterol levels that are considerably higher than the normal, and also, that the cholesterol levels of such individuals tend to fluctuate between wider than normal limits.[24, 25] On the other hand, the picture is blurred by the fact that the vast majority of people presumably developing atherosclerosis have blood cholesterol levels that fall within the accepted normal range. Indeed, numerous investigations have been unable to demonstrate that an elevated blood cholesterol level is an essential prerequisite to the development of atherosclerosis.[26-28] The normal range of blood cholesterol, too, has been, and to an extent still is, a much debated question. In most clinical laboratories the normal figures usually cluster about 200 mg./100 cc., though some workers regard levels up to 350 mg./100 cc. as being within the normal span. In this connection, Gould[29] has pointedly observed that, when compared to the very much lower levels for blood cholesterol normally present in most animals, even a figure of 200 mg. may be considered excessive, and he puts forward the disturbing suggestion that our so-called normal figures may actually represent a state of chronic hypercholesterolemia.

The evidence that atherosclerosis is causally related to a disturbance of lipid metabolism rests in large measure upon studies of the disease in experimental animals, notably those concerned with cholesterol-induced arterial lesions in rabbits, though in some quarters these studies

have been unthinkingly maligned and their true significance minimized. In 1913 Anitschkow[30] made the startling discovery that if rabbits are fed one-half to one gram of cholesterol per day they soon manifest striking elevations of blood cholesterol, and, after some weeks, develop intimal lesions of the aorta and other major arteries that in morphology and lipid content bear a remarkable resemblance to the naturally-occurring lesions encountered in human beings. To be sure, there are some differences between the experimentally-induced disease in rabbits and that seen in man; these involve chiefly differences in distribution, the lesions being more prominent in the thoracic aorta and pulmonary artery in the rabbit, whereas in man the abdominal aorta is more severely affected and the pulmonary artery spared; and also the fact that the arterial lesions in the rabbit are almost invariably associated with sustained hypercholesterolemia and are usually preceded by the deposition of lipid in the reticulo-endothelial system and other viscera.[31] The major objection to these experiments is based on the assumption that the rabbit being an herbivorous animal lacks metabolic facilities to handle cholesterol, a substance normally foreign to its diet, and consequently, when this foreign material is included in the diet, it is precipitated in various organs and blood vessels. This cogent argument was utilized effectively by those who felt that observations made on atherosclerosis in rabbits were not transposable to the disease in human beings. During the past few years, however, the ground on which this objection was founded has been largely cut away. In 1942, Dauber and Katz[32] succeeded in producing atherosclerosis in the chick, an omnivorous animal, by adding supplementary cholesterol to the diet; and subsequently, Kendall and his associates[33] produced atherosclerosis in the dog, a carnivorous animal, by suppressing thyroid function with thiouracil and adding cholesterol to the diet. Furthermore, recent studies employing isotopic tracers have demonstrated beyond doubt that, herbivorous though they be, rabbits are capable of synthesizing and metabolizing large quantities of cholesterol.[21, 34] It would appear from the accumulated evidence, therefore, that the cholesterol-induced arterial lesions in rabbits, and also those in the chick and the dog, while perhaps not precise counterparts of the atherosclerosis of human beings, are nevertheless so similar as to suggest the operation of closely allied, if not identical, pathogenetic factors. Yet the mechanism whereby cholesterol feeding induces atherosclerosis in the experimental animal remains undisclosed, and a number of facts make

it seem doubtful that elevated blood cholesterol is alone responsible for the development of the disease.[35]

At this point we must digress momentarily to survey the rapid advances in lipid chemistry made possible quite recently by the availability of elegant new tools and techniques – heavy water, radioactive isotopes, electrophoresis, and the ultracentrifuge, to mention but a few. It has become apparent that cholesterol, once considered to be chemically inert and metabolically inactive, is an essential constituent of the mammalian cell and an extremely active metabolite. The evidence is now clear that many tissues can synthesize cholesterol both in vivo and in vitro from simple and readily available precursors such as acetate radicals;[29, 36] that there is a surprisingly rapid interchange between the cholesterol of plasma and that of the liver and other tissues;[29] and also, that the organism as a whole has metabolic facilities not alone for excreting but also for breaking down the cholesterol molecule.[37] It is estimated that human beings may synthesize as much as 1500 to 2000 mg. of cholesterol per day,[29] an amount, it is worth noting, far in excess of the average dietary intake. Similarly, evidence is now at hand for synthesis and active metabolism of the phospholipids and fatty acids, though it would take us far afield to catalogue in detail these and other impressive advances in lipid chemistry.

One area of investigation, however, concerned with the question of lipid transport, is germane to our central theme, for the progress made in this field quickly enriched our understanding of atherosclerosis. A problem that has long perplexed chemists and biologists is the mechanism whereby blood plasma, essentially an aqueous medium, can maintain in exquisitely clear solution so large a quantity of lipid, since there are normally in each 100 cc. of plasma some 500-800 mg. of cholesterol, cholesterol ester, phospholipid, and neutral fat – all compounds which in their pure state are virtually insoluble in aqueous media. Light has recently been thrown on this problem by the work of Boyd,[38] confirmed and extended by Ahrens and Kunkel,[39] which points to the phospholipids as being important in maintaining the stability of the plasma lipids; these workers have demonstrated that plasma remains clear even at abnormally high cholesterol and neutral fat concentrations so long as the phospholipids are concomitantly elevated, whereas the emulsion is unstable and the plasma appears milky if the relative phospholipid content is low. Still more recently, certain plasma proteins have been

found to be intimately concerned in the process. This relationship was first hinted at by the imaginative studies of Macheboeuf;[40] it has been enlarged and placed on a firm and quantitative basis by investigations made in the laboratories of Tiselius in Sweden[41] and Cohn in this country.[42] From these studies it now seems probable that the bulk, if not all, of the plasma lipids are present in combination with protein. Indeed, Oncley and his coworkers[43] have elaborated chemical techniques for the separation of two lipoproteins from human plasma, identified electrophoretically as alpha and beta globulins, which between them contain almost all the plasma lipids, and further, the beta-lipoprotein has been purified and found to be soluble in aqueous media despite the fact that it is composed largely of lipid. How these important new facts concerning lipid transport bear upon the problem of atherosclerosis will appear as we scrutinize some recent observations made on the disease in experimental animals and in man.

It has been noted by several groups of workers[44, 45] that in normal rabbits the blood phospholipid level is usually somewhat higher than the cholesterol level, whereas in cholesterol-fed rabbits with atherosclerosis, this situation is reversed, the blood cholesterol level being regularly much higher than the phospholipid. In view of the part played by the phospholipids in stabilizing the serum lipid emulsion, it was suggested that this disparity between cholesterol and phospholipid might be an important factor in the development of experimental atherosclerosis. A means of testing this hypothesis became available when it was found that certain surface-active agents when injected intravenously produced, among other things, marked and sustained elevations of the blood phospholipid content.[46] Accordingly, an experiment was performed in which rabbits fed a high-cholesterol diet were given repeated intravenous injections of the surface-active agents Tween 80 or Triton A-20. The injected animals developed far less atherosclerosis than did uninjected control animals fed the same cholesterol diet, and it is of interest that the degree of atherosclerosis could be correlated with the blood phospholipid level; the injected animals had high phospholipid as well as high cholesterol levels, in sharp contrast to the controls in which the cholesterol levels were comparably elevated but the phospholipid levels distinctly lower.[47] Similar findings have now been reported by Duff and his colleagues,[48] who also found that the protective effect of alloxan diabetes against the development of cholesterol-induced athero-

sclerosis in rabbits, previously discovered by them, could be correlated with elevated phospholipid and neutral fat levels.[49] Moreover, the clinical studies dealing with blood phospholipids done by Ahrens[50] in patients with biliary obstruction, those of Gertler[51] in patients with coronary artery disease, and those of Eilert[52] in women receiving estrogenic hormone therapy, though not conclusive, do suggest that the cholesterol-phospholipid ratio may be a factor in the atherosclerosis of human beings as well. These clinical and experimental findings serve to focus attention upon the physico-chemical state of the blood lipids and upon the interrelations between the various lipids, rather than upon the absolute level of the blood cholesterol, as being important determinants involved in the pathogenesis of atherosclerosis.

During the past two years the picture has acquired more detail with the appearance of the ingenious and provocative studies of Gofman and his associates[53, 54] These investigators using the analytical ultracentrifuge found that all the major lipids in the serum are transported in the form of giant lipid-protein complexes which can be characterized and quantitated by their ultracentrifugal flotation properties. The pattern of these lipoprotein molecules, though differing widely from one individual to another, is quite constant under normal conditions for any one individual during prolonged periods of time, and is subject to modification by diet, disease, and certain drugs. While these complexes are more common in hypercholesterolemic sera, they may, and very frequently do, occur in the sera of patients with normal or even low cholesterol levels. Further, these workers observed that one portion of the spectrum of these large lipoprotein aggregates, those classified in the S_f 10-30 category, are regularly associated with the development of experimental atherosclerosis in cholesterol-fed rabbits, and similarly, the molecules in the S_f 12-20 range appear to bear a strong correlation to the development of the disease in human beings. Comparison of a large group of normals with a matched group who had suffered myocardial infarction reveals a significantly greater incidence of excessive concentrations of these abnormal molecules in the sera of the latter group. Moreover, these workers maintain that the level of S_f 12-20 molecules in the blood may serve to designate, years in advance of its clinical manifestations, those who are susceptible to severe atherosclerosis, and may be useful as a means of estimating prognosis and evaluating therapy following myocardial infarction. It is noteworthy that females, especially in the

early and middle age groups, have in their sera far lower concentrations of these molecules than do males, a fact which may account for their relative freedom from clinical atherosclerosis. Graham, working in Gofman's laboratory, has recently reported[54] that injection of heparin into human beings and experimental animals brings about a dramatic reversal toward normality in the serum lipoprotein picture, and that repeated injections into rabbits protects them against the atherosclerosis of cholesterol feeding. It is of interest that the effect of heparin is apparently unrelated to its anticoagulant action. This intriguing observation, quite apart from its possible therapeutic implications, may provide a clue to understanding the metabolic relations involved in the formation of lipoprotein complexes. Despite the recognized difficulties of quantitating atherosclerosis in human beings — for neither clinical, radiographic, nor even post-mortem estimates are wholly reliable — and despite the acknowledged pitfalls in finding an adequate control series for a disease which is practically universal, it must be stated that the association between the serum concentration of these large lipoprotein molecules and the development of severe atherosclerosis is more impressive than any that has hitherto been demonstrated. Whether these molecules are themselves the offending agent in atherosclerosis or whether they represent an epiphenomenon, a reflection of a more ultimate cause, remains to be determined. It is nevertheless becoming increasingly clear from these researches, and from the parallel studies of Barr, Russ and Eder[55] using chemical techniques to fractionate plasma lipoproteins, that in atherosclerosis there is an underlying lipid metabolic defect, one of the manifestations of which is an aberration of lipid transport which appears to promote the deposition of lipid within the intima of blood vessels.

Attention has been drawn for a long time to the possible role of dietary factors in the causation of atherosclerosis. The question has frequently been raised whether over-abundant diet, rich in fatty and cholesterol-bearing foods, may not be responsible for the alarming incidence of atherosclerosis in our society. In brief, are we eating our way to atherosclerosis? A decisive answer to this question is not forthcoming at the present time. The post-mortem studies of Wilens[56] and the experimental observations of Firstbrook[57] point to a correlation between overnutrition and atherosclerosis. The level of blood cholesterol, though little influenced by moderate fluctuations in the cholesterol or fat con-

tent of the diet,[58] may be appreciably reduced by rigid restriction of both, as in the rice diet.[59, 60] It is a curious fact, however, that addition of vegetable fat containing no cholesterol to such a severely curtailed diet causes a return of the blood cholesterol to previous levels, making it plain that elimination of cholesterol-containing foods from the diet is not effective unless the total fat content of the diet is stringently reduced at the same time.[58, 61] It has been pertinently said of atherosclerosis that if cholesterol is the culprit, fat is an active accomplice.[62] Gofman has studied the effect of diet on the lipid transport mechanism, and he has reported a decrease, and on occasion even disappearance, of the S_f 12-20 lipoprotein molecules from the blood of individuals placed on diets of low fat and low cholesterol content.[54] Such diets have in fact been advocated as having beneficial effects in atherosclerosis, though the evidence for this is still quite incomplete. In connection with dietary factors one must consider the lipotropic agents, especially choline and inositol, which, because of demonstrated effectiveness in reversing the fatty liver of certain nutritional deficiencies and perhaps also because they are essential constituents of the major blood phospholipids, have been advocated and widely employed in the therapy of atherosclerosis.[63] The results of clinical trials, however, are unconvincing; and the use of these agents in experimental animals has repeatedly been found unsuccessful in raising blood phospholipid levels or in affecting appreciably the development or resorption of atherosclerosis.[64-66] Thus, additional clinical and experimental data are required before the role of diet and specific dietary factors in this disease can be accurately assessed.

Lest we become so preoccupied with the chemistry of lipids that we lose sight of the blood vessels where the disease actually strikes, mention must be made of the operation of other factors which, though perhaps ancillary, are nevertheless important in a full understanding of atherosclerosis as a pathological process. It seems quite probable from studies on the permeability of the endothelium that there is a constant flow of plasma filtrate containing lipids and many other substances across the endothelium into the interstices of the vessel wall,[67] whence they are removed via lymphatics or vasa vasorum by mechanisms as yet undisclosed. Interference with these removal mechanisms may well account for the localization of atheromata at sites of injury to the vessel,[68] and also at points of fixation and branching, and, in like manner, may explain the propensity of syphilis to enhance the severity of atherosclerosis in the

thoracic aorta.[69] Intravascular pressure is unquestionably another factor in the localization of atheromata, lesions being most common at points of high pressure and scarce or absent where pressure is low. Thus, the systemic arterial tree is most vulnerable, the pulmonary circulation distinctly less so except in instances of pulmonary hypertension, and the veins virtually unaffected by the disease, though, needless to say, the lipid composition of the plasma is essentially the same in all compartments of the arterial and venous channels. That increased blood pressure may also augment atherosclerosis has recently been demonstrated experimentally by Wakerlin.[70] Dogs were made hypertensive by the Goldblatt technique and then fed a diet containing cholesterol and thiouracil; these animals developed atherosclerosis at a strikingly accelerated rate as compared with that of normotensive controls fed the same diet. It should be noted in this connection that dogs with sustained hypertension for many years do not develop atherosclerosis in the absence of the disturbed lipid metabolism induced by the diet. The effect of pressure is thought to derive from increased filtration through the vessel wall, which, if the underlying lipid defect of atherosclerosis is present, serves to hasten the deposition of lipid. It may be that such a mechanism is responsible, in part at least, for the well recognized clinical fact that hypertensives, both male and female, are particularly susceptible to atherosclerosis and its more serious complications.[71]

"Science," Conant[72] has stated, "advances not by the accumulation of new facts, . . . but by the continuous development of new and fruitful concepts." Judged by this standard, substantial progress has been made in our understanding of atherosclerosis. The happenings of the past few years, herein briefly recounted, surely attest to the profound stirring that is now perceptible in this field. Numerous investigators armed with wondrous new tools are probing deeply into the vital chemistries of tissues and cells. An abundance of new facts has been wrested from nature, and based on them there have been erected dynamic and fruitful concepts that bode well for the future and hold much promise for clinician and experimentalist. As a result of these advances, the attitude of hopelessness about the disease is giving way to one of quiet optimism that in atherosclerosis prevention and, indeed, even therapy may be attainable.

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SURGICAL REVISION IN CONGENITAL CARDIOVASCULAR DISEASE*

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Of all of the physiologic systems which in later life are so intricately interwoven to form the complete organism, the cardiovascular system is the earliest to become functionally differentiated in the embryo. Unlike the nervous, skeletal, digestive, or urogenital systems, it becomes functional almost as soon as it forms, and on its continued and uninterrupted function life itself depends. From the time, approximately 14 days after fertilization, before which the developing ovum depends on simple osmosis for its metabolic exchange, until the revolutionary physiologic changes which follow birth and independent life, first the chorion and then the placenta carry on by means of the circulatory system the activities of digestive system, kidney, and lung while these organs develop without function. In order to be able to carry on this vital role so early in embryonic life, it is evident that the tissues of the circulatory system cannot be highly specialized. It is not surprising therefore that these tissues retain much of their primitive vigor throughout life until eventually their degeneration becomes synonymous with senescence itself.

The circulatory system goes through a complicated evolution, which not only reproduces in anatomic pattern a phylogeny of almost inconceivably remote antiquity but which also is subject to arrests or aberrations in development at almost every stage. The resultant abnormalities, if not of such an extent that fetal life cannot continue, are termed, after birth, congenital anomalies, or they are given the misnomer of congenital heart disease. It is important, especially from the surgeon's viewpoint, to remember that disease in the sense of a noxious or destructive agent attacking normal tissue is not present. The tissues are normal; they are simply arranged in an abnormally atavistic or bizarre anatomical pattern

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which interferes more or less seriously with normal function. It is this fact which renders these conditions peculiarly amenable to surgical correction if suitable techniques can be devised to rearrange the pattern to one which is nearly or quite normal, or, failing that, to one which permits more nearly normal physiologic function.

It is not the purpose of this presentation to discuss the manifold aberrations in development of peripheral vessels. Most of these are of little clinical importance except for large or multiple abnormal arteriovenous communications, and they are usually, if it is possible, best treated by simple removal. In this field there is little that is not well known and less that is new. But recently great advances have followed development of surgical and anesthetic techniques which permit more or less lengthy and meticulously careful surgical manipulations within the thorax. In this region the surgeon can now approach directly and at leisure anomalies of the major vessels and, within expanding limits, anomalies of the heart itself.

It has been customary to classify the more frequent of these anomalies in a descriptive way, labelling them with the names of those who first called attention to a particular pattern, or by the pathologic term of the most conspicuous anomaly and pigeon-holing them in no coherent order. But as we become more familiar with the great variation in pattern seen in the operating or autopsy room, these arbitrary categories tend to break up into numerous subdivisions which merge into each other or combine in multiple variations which defy rigid classification. Yet some order must be achieved if we are to discuss them in practical terms and especially if we are to approach them in a way which will permit us to separate out those which can be revised from those which cannot. This is even more necessary if new answers are to be found to previously unanswered problems.

A logical approach can perhaps be made by first separating out those anomalies which merely represent persistence into post-natal life of a vascular or intracardiac pattern which is normal at some stage before birth. These anomalies represent failures in normal involution (Table I).

The next group might include those anomalies which result from the abnormal involution of structures which normally persist, or combinations of these with persistence of structures which normally involute (Table II). Finally, there is a group in which the course of development is abnormal from the beginning. These do not represent

TABLE I—PERSISTENCE OF NORMAL FETAL ANATOMY
(Failure of Normal Involution or Development)

A. Patent Ductus Arteriosus
B. Patent Foramen Ovale
C. Persistent Left Superior Vena Cava (entering coronary sinus)
D. Double Aortic Arch
E. Patent Interatrial Foramen (Auricular Septal Defect)
F. Ventricular Septal Defect
G. Persistent Truncus Arteriosus
H. Common Ventricle (Pre-reptilian Heart)

TABLE II—INVOLUTION OF STRUCTURES WHICH NORMALLY PERSIST, ALONE OR ASSOCIATED WITH PERSISTENCE OF STRUCTURES WHICH NORMALLY INVOLUTE

A. Coarctation of aorta

B. Right aortic arch and associated anomalies

C. Right subclavian originating from descending aorta

D. Right-sided or bilateral ductus arteriosus

E. Valvular stenosis
   1. Tricuspid: Rudimentary right ventricle, pulmonary atresia, auricular septal defect
   2. Pulmonary: "Pure," with patent foramen ovale
   3. Mitral with auricular septal defect—Lutembacher's syndrome
   4. Aortic: subaortic stenosis

F. Infundibular stenosis with failure of closure of ventricular membranous septum—Tetralogy of Fallot

G. Atresia of pulmonary artery with failure of closure of ventricular membranous septum

TABLE III—ABNORMALITIES OF DEVELOPMENT

A. Pulmonary vascular anomalies
   1. Aberrant arteries from aorta
   2. Pulmonary veins entering vena cava or right atrium
   3. Vena cava entering pulmonary vein or left atrium

B. Abnormal origin of tricuspid leaflets with interatrial defect (Ebstein's complex)

C. Over-riding aorta without transposition (Eisenmenger's complex)

D. Transposition of great vessels (with associated anomalies)

E. Dextrocardia (dextrorotation or situs inversus with levorotation)

TABLE IV

Fetal Age	*Group I*	*Group II*	*Group III*	
Term	Ductus Arteriosus Foramen Ovale Left Vena Cava			
	Double Aortic Arch	Coarctation Right Aortic Arch Right Subclavian from Descending Aorta Right or Bilateral Ductus		Correctable or Harmless
12 mm	Interatrial Foramen* Membranous Septal Defect†	Valvular Stenoses† Infundibular Stenosis‡*	P.V.A.	Partially Correctable
7 mm	Interventricular Foramen* Truncus Arteriosus‡ Common Ventricle‡	Atresia of Pulmonary Artery‡	Ebstein's* Eisenmenger's‡ Transposition‡ Dextrocardia‡	Not Correctable

*Cyanosis inconstant
†Cyanosis variable or late in appearing
‡Cyanosis constant and deep

any stage through which the fetus normally passes, but the stage of fetal development at which they originate can still be determined through knowledge of the time relationships of normal development (Table III). It should be emphasized that combinations of all three groups are frequent. Indeed, the presence of an anomaly of the third group, most of which originate very early in fetal life, may be a factor in altering the normal development pattern of other structures later on.

If we now arrange these groups in parallel columns and list them in approximate chronological order in terms of fetal development, certain obvious generalizations immediately become apparent. These may be helpful not only in bringing the jumble of apparently arbitrarily defined yet overlapping anomalies into a comprehensible order, but also in understanding the fundamental relationships of the various conditions to the possibilities for their correction (Table IV). It immediately becomes evident, for example, that the later is the stage in fetal development which the anomaly represents, the better is the prognosis. Anomalies representing failure of involution of structures normally present

in a 10 or 12 mm. embryo are for the most part correctable by surgery (for example patent ductus and double aortic arch) or they cause little physiologic disturbance (patent foramen ovale). In the second group, likewise, anomalies caused by involution of structures which usually persist combined with persistence of structures which usually involute, if their origin does not go back of the 12 mm. embryo either cause no symptoms (right aortic arch) or they can be completely corrected by operation (coarctation of the aorta).

If, however, there are anomalies originating at an earlier stage, the problem becomes more difficult. Correction of stenosis of the pulmonary valve can now be at least partially achieved by the procedure devised by Brock, but no sure way has yet been found to overcome congenital stenoses of the other valves and the anomalies usually associated with them. The immediate brilliant results obtained in Tetralogy of Fallot by creation of an artificial ductus are achieved by introducing a compensating abnormality which in many cases creates a more nearly normal physiologic function without correcting the anomaly itself. It is not yet certain whether this balanced abnormality can be maintained indefinitely. Abnormalities which originate earlier than the 7 mm. embryo, in which nearly all of the third group fall, have as yet not been substantially helped by operation.

It is also apparent that those lesions which produce deep and constant cyanosis for the most part originate very early and cannot be corrected, while those in which cyanosis is variable, inconstant or late in appearing are related to anomalies of a later developmental stage, in some of which spectacular physiologic improvement can be obtained by operation even though a normal anatomic pattern is not restored. It is this group in which further advances seem most likely to be made.

Let us review then briefly, the present status of surgical revision of these anomalies.

Persistent Patency of the Ductus Arteriosus heads the list. It is a condition which is normal at birth, and becomes abnormal only when post-natal involution fails to occur. It is also the first of all of these anomalies to have been successfully corrected, and it is now the anomaly in which complete restitution to normal is accomplished with least risk. The symptoms which result from persistent patency of the ductus arteriosus vary with the size of the opening. When it is small they may be negligible, at least in childhood and youth, but when the opening is

large, allowing correspondingly large abnormal flow of blood from the aorta back into the pulmonary artery, the effects on health may be profound. Yet even in the apparently symptomless individual unexpected improvement often follows closure of the ductus, and it seems probable that life expectancy is prolonged.

The diagnosis is usually not difficult, for in the great majority of cases after infancy a characteristic machinery-like murmur is readily heard over the pulmonary area. Those cases in which the murmur is unusual are usually instances in which the ductus is very large and the abnormally high pressure in the pulmonary arteries has resulted in sclerosis and in a reduction in diastolic flow through the ductus, or even a reversal of flow. In such cases the diagnosis can be made from history, roentgenographic and electrocardiographic findings, or, if necessary, by catheterization of the right heart and pulmonary artery.

Whether the ductus should be closed by division of the vessel and suture of the cut ends, or by simple double ligation in continuity is still a matter of discussion. Division and suture is probably a more certain method of insuring permanent closure, but carries a somewhat higher risk. It is rare for a new channel to form when double ligation is properly carried out, and the risk of this procedure in competent hands is very slight. In the presence of late complications, however, the risk is much increased. Associated subacute endarteritis, though curable by operation alone, is usually more safely handled by control of the infection with antibiotic treatment, followed by closure of the ductus after the patient has been restored to comparative health. When myocardial failure or reversal of flow has supervened, the risk is high, yet the prognosis in such cases is usually so poor that the attempt must be made. Thus it is now generally agreed that operation is indicated in practically all cases of patent ductus arteriosus.

Coarctation of the Aorta is the next anomaly to yield to surgical correction. It represents a relatively minor deviation from the normal pattern of involution, and complete restitution to normal can usually be accomplished. Like persistent patency of the ductus arteriosus its effects vary with the severity of the lesion. When the aorta is completely closed, the resulting hypertension above the closure and decreased ability of the circulation below to meet sudden or heavy demands will become apparent early in life. Mild constrictions, on the other hand, may cause no obvious symptoms, and often escape detection until late

complications develop.

Here again the diagnosis is readily made if the condition is suspected. Increased arterial pressure in the arm, contrasted with absent pulse or diminished pressure in the legs is characteristic. A systolic murmur is usually present, but it may be inconspicuous and is usually of little diagnostic help. Characteristic notching of the ribs by the enlarged and tortuous intercostal collaterals is often seen on chest roentgenograms but is not always present especially in children. Special diagnostic techniques are usually not necessary. Ballistocardiographic tracings show a characteristic abnormality in the pulse wave pattern and are useful not only in judging the severity of the lesion but also in evaluating the effectiveness of operative relief. Retrograde angiograms not only confirm the diagnosis but localize the lesion and give an indication of its extent.

The risk of operation, involving excision of the coarcted segment and end-to-end anastomosis of the aorta, is a real one but in competent hands it is steadily diminishing. After childhood degenerative changes in the vessel wall add to technical difficulties, increasing the risk. In such cases alternate procedures may be necessary such as the use of the enlarged left subclavian or an aortic graft to bridge a gap, measures in which the ultimate outcome is still uncertain, although the immediate results are promising. There is some question as to whether a coarctation, corrected in early childhood, may recur due to failure of the anastomosis to grow with the growing aorta. Experimental evidence now indicates that this fear is unfounded if continuous sutures of nonabsorbable material are avoided.

As in the case of patent ductus, it seems probable that individuals with coarctation of the aorta, even when there are no apparent symptoms, suffer a subtle handicap which increases with the years and often leads to premature death through complications in middle age. Since the risk of operation is not great in childhood, but increases rapidly after maturity, it is to be hoped that the condition will in the future be recognized early and operative correction carried out even in the absence of symptoms.

Anomalies of the Aortic Arch, in contrast to the previous abnormalities, cannot be surgically restored to a normal anatomic pattern. They occur rarely, and many are of little clinical interest since they cause no real disturbance in circulation. When symptoms do occur, it

is usually because pressure or constriction of other organs is caused by the presence of anomalous arteries. Variations are so great that it may almost be said that no two situations are identical, yet certain patterns associated with recognizable symptoms and signs are sufficiently frequent to merit discussion, especially since operative relief is often possible.

Double Aortic Arch, a simple persistence of a normal fetal stage, results from failure of the right arch to involute between the subclavian and the point of juncture of the two primitive descending aortae. If this point remains sufficiently distal to the arches, no symptoms will result, and the condition will be discovered unexpectedly at autopsy or operation. It may also be recognized on roentgenograms. If, however, the arches join high, a rigid vascular ring is formed about the trachea and esophagus which interferes more or less seriously with breathing, swallowing, or both.

Usually symptoms develop early in infancy. A more or less constant stridor, worse during upper respiratory infections or with vigorous breathing, as in crying, should raise the question. Cyanotic attacks during feeding are also common, due to the fact that the esophagus can be distended only by pushing forward the membranous portion of the trachea. Occasionally real esophageal obstruction is also a problem, especially with solid foods which pass only with difficulty through the angulated esophagus.

The diagnosis can sometimes be made by recognition of compression or angulation of the tracheal air column on a lateral roentgenogram. Usually demonstration of the deformity is more apparent if the trachea is outlined by iodized oil. Similarly a barium swallow will show characteristic forward angulation and usually a lateral distortion of the esophagus. If necessary, a more accurate demonstration of the exact pattern of the vessels can be obtained by retrograde angiography, but this is a procedure of some technical difficulty in a small infant and not without risk if the patient is in poor condition, as is often the case.

Other Aortic Arch Anomalies may also result in a vascular ring around the trachea and esophagus. Usually the primary disturbance is persistence of the right aortic arch, with abnormal involution of the left. The latter may remain as a fibrous cord joining a left innominate to the descending aorta. In other cases the ligamentum arteriosum may complete the ring by entering the descending aorta as it crosses behind

the esophagus. The ring so formed is looser than that due to double arch because the pressure in the pulmonary artery is less and the vessel in consequence is softer. But if the ductus remains patent, aortic pressure is transmitted through it to the pulmonary artery and real obstruction results.

Distortion of the esophagus is also caused by anomalies which do not form a true vascular ring, and occasionally, these are of sufficient degree to cause serious dysphagia. Simple persistence of the right aortic arch with involution of the left, though it causes a characteristic slight distortion of the esophagus, does not by itself, have any clinical significance. The most frequent of these anomalies to cause symptoms is due to involution of the segment of right arch between carotid and subclavian with persistence of the segment from subclavian to the point of aortic junction. This results in a long vessel originating from the descending aorta, passing behind the esophagus and ending as the right subclavian. Another is due to an abrupt crossing over behind the esophagus of a persistent right arch associated with a normally placed descending aorta. Variations in this group are the rule, and exact anatomical diagnosis may not be possible before operation.

In correcting the effects of these anomalies the surgeon must be guided by knowledge of the embryologic possibilities, and take care to release the trachea and esophagus by dividing the ring in such a way that no vital vessel is disturbed. In the case of a double arch the left arch can usually be cut between left carotid and left subclavian, though sometimes it is more expedient to divide it below the subclavian. It is necessary to select carefully the arch to be divided since not infrequently it may be found that a coarctation exists in one of them. Either subclavian may be sacrificed. If the ring is due to a ligamentum arteriosum or patent ductus, division of this structure will suffice. Often the aperture can be widened by pulling the vessel which crosses the front of the trachea forward and attaching it to the sternum, but since this is usually the base of the left carotid, it is dangerous to resect it. Indications for operation depend upon the severity of the symptoms and early recognition of the condition, before the infant's condition has become critical and while the risk is not high. Too often, however, the condition is not appreciated until after numerous episodes of pneumonia have added greatly to the risk.

Anomalies of the Pulmonary Vessels are rare lesions in which no

single pattern stands out as a clinical syndrome. Pulmonary arteries arising from the aorta or other systemic vessels have been described in great variety. Usually they are isolated anomalies associated with abnormal lung lobes and do not cause physiologic disturbance of the circulation though they may be associated with pulmonary anomalies requiring resection. Occasionally, systemic veins may enter the pulmonary system, especially a persistent left vena cava. They usually cause little disturbance. When they are found incidentally in the course of operation for other anomalies, they can be divided in most instances without hesitation.

When one or more of the pulmonary veins enters one of the venae cavae or right atrium, however, the resultant overloading of the right heart may be serious unless there is a large interatrial septal defect. Although theoretically an ideal correction would be a re-implantation of the anomalous vein into the left auricle, this is rarely feasible technically. Blalock has recommended creation of a large communication between the auricles for this situation. If only a single vein is involved, removal of the corresponding lobe, or even an entire lung may be justified.

Intracardiac Anomalies as a group pose quite a different problem from those of the great vessels. Arising from arrests or abnormalities at an earlier stage of fetal development, they also less often occur as single lesions. In addition, the necessity of manipulating a sensitive and active organ without seriously interfering with its constant function still sharply limits the possibilities of successful surgery.

Septal Defects, especially those in the auricular septum due to persistent patency of the interatrial foramen, the effect of which may often ultimately be severe, seem to be the most likely of the intracardiac lesions of the first group to be correctable. Much interesting experimental work is in progress, but as yet no method has been perfected which has been accepted as clinically useful.

Pulmonary Stenosis, a term broadly used for a variety of lesions primarily of the second group, has been approached surgically with more success. In general, these conditions have in common combinations of anomalies which on the one hand restrict the flow of venous blood from the right heart to the lungs, and on the other divert a greater or less amount from the right heart into the left and so into the arterial tree. As a result cyanosis is usually present.

Pure Pulmonary Stenosis may occur as a single lesion due to fusion of the cusps of the pulmonary valve without any other anomaly. Such patients are not cyanotic at rest since all blood entering the right heart chambers must leave through the narrowed pulmonary channel. The result is an enormous increase in work load of the right ventricle which it meets by marked hypertrophy and development of a very high ventricular pressure. Even so the right heart frequently is unable to meet the demands of normal exertion with resultant dyspnea and rise in venous pressure. The latter, through distension of smaller venous channels, may produce transient cyanosis of venous origin, but arterial unsaturation does not occur, and dyspnea is due to hypercapnia rather than to anoxia.

More often, when the pulmonary valve cusps are fused, there is from birth sufficient back pressure in the right atrium to hold the foramen ovale open, and to permit, especially during exertion, decompression of the right heart by shunting part of the venous return into the left. Cyanosis of arterial unsaturation therefore results. Although this situation is also termed "pure" by Taussig in order to distinguish it from the more complex forms of pulmonary stenosis, it is not a single lesion.

These two forms of "pure" pulmonary stenosis have much in common, being distinguished clinically only by the presence or absence of arterial unsaturation. Both result in loud harsh systolic murmurs in the pulmonary region with absence of the second sound. Cardiac enlargement varies from almost none to very great in advanced cases, but evidence of right ventricular hypertrophy is always present on electrocardiogram and usually on roentgenographic silhouette. The latter also frequently demonstrates a dilated pulmonary artery shadow at the base of the heart in contrast to diminished vascular markings in the lung fields. This feature helps distinguish this from the pulmonary stenoses of earlier developmental origin in which the arterial shadow is usually small or absent. Catheterization shows an increased right ventricular pressure in proportion to the degree of stenosis, and a much damped pressure in the pulmonary artery if the catheter can find its way through the valvular orifice. The "purity" of the anomaly is proved if pressure is higher than that in the systemic arteries and if saturation in the outflow tract is the same as in the atrium.

Brilliant results are now obtainable in pure pulmonary stenosis by Brock's method of dividing the fused valve and stretching it with

sounds. This procedure does not completely restore normal anatomy since the valve is still abnormal, as demonstrated by persistence of the murmur. But that nearly normal valvular function and pressure relationships can be achieved is shown by postoperative catheterization studies. Thus a seriously disabling anomaly is converted to one of minor consequence. If a patent foramen ovale is also present, this anomaly is, of course, not changed, but the altered pressure relationships convert the flow through it from predominantly right to left to the reverse, thus eliminating cyanosis.

The risk of pulmonary valvulotomy may be high if the patient is close to right heart failure. In an early, well compensated case the operation is usually well borne in spite of the fact that it involves passing a succession of instruments through the right ventricular wall. This means that decision may be difficult in a child without cardiac enlargement or cyanosis and in whom the only symptom is dyspnea on exertion.

Tetralogy of Fallot is a combined anomaly, incorporating elements of all three groups. Failure of the membranous interventricular septum to close, a simple persistence of a normal fetal stage, is perhaps merely a secondary effect of the stenosis of pulmonary outflow tract which is usually in the infundibular portion of the right ventricular wall, though it may be at the valve as in pure pulmonary stenosis. Typically there is also an abnormality of aortic origin such that it seems to arise partially from both ventricles, straddling or "over-riding" the incomplete ventricular septum and receiving blood from both ventricles. This "dextroposition" or partial transposition of the aorta is an anomaly of the third group, not normal at any stage of fetal development and possibly due to unequal division of the primitive truncus arteriosus. Its extent varies greatly in different individuals.

The term tetralogy of Fallot is primarily a descriptive one, referring to the four features which combine to form the syndrome; dextroposition of the aorta, pulmonic stenosis, ventricular septal defect, and right ventricular hypertrophy. Since it is not a true entity, its manifestations vary widely depending on which anomaly is preponderant. If aortic transposition is preponderant and pulmonic stenosis is slight, there will be deep and almost constant cyanosis due to the ease with which right ventricular blood enters the aorta, rather than the difficulty with which it enters the pulmonary artery. The result may be a situation very

similar to Eisenmenger's syndrome, which differs anatomically only in the complete absence of pulmonary stenosis. Such a patient can be helped relatively little by operation.

On the other hand if the aortic over-riding is slight, the membranous septal defect small, and the obstruction to pulmonary flow the major factor, the result will be similar to that seen in "pure" pulmonary stenosis. In both situations cyanosis is almost absent at rest, but deepens during exertion through "overflow" from the right heart into the left. Indeed those patients in this group in which the obstruction to pulmonary flow is due to valvular stenosis can best be treated by the Brock procedure. In the majority, however, stenosis is in the infundibular region. Although a direct approach to such a lesion is being investigated by Brock and by Glover, their results are not yet sufficiently consistent to warrant general use. In most cases establishment of a shunt between systemic and pulmonary circulation, as demonstrated by Taussig and Blalock, gives satisfactory and striking relief.

In making the diagnosis, tetralogy must be differentiated not only from the Eisenmenger syndrome and "pure" pulmonary stenosis but also from other anomalies causing cyanosis. Most of these anomalies are of very early origin, falling in all three groups. Common ventricle, persistent truncus, atresia of the pulmonary artery, Ebstein's syndrome and transposition of the great vessels are in this group, and more complex combined anomalies are frequent. A distinguishing feature is the constancy of the cyanosis in the latter group, as contrasted to the variable cyanosis in most cases of tetralogy. The character of the murmurs is of little help, but absence of murmur practically rules out tetralogy. In addition, heart size and contour on roentgenogram or fluoroscopy is of considerable importance, for the more primitive anomalies usually result in large globular hearts, whereas the heart in tetralogy is rarely enlarged and often presents a characteristic "boot-shaped" contour. Angiocardiograms demonstrate that the right ventricle empties into the aorta, but this may occur in other anomalies. On occasion it may also demonstrate the point of infundibular narrowing. Cardiac catheterization is very useful when the diagnosis is obscure, since from data so obtained the difference in flow between pulmonary and systemic circulation can be calculated. This is of great assistance in distinguishing tetralogy from Eisenmenger's complex, and excluding the presence of a compensating patent ductus arteriosus. It cannot differentiate atresia

of the pulmonary artery, however. In general, as Taussig has emphasized, in the majority of cases it is not necessary to resort to the more complicated diagnostic procedures, though they may give a useful measure of the severity of the abnormality and the chances of success in surgical treatment.

The Blalock-Taussig procedure consists in establishing a new channel from a systemic artery into the pulmonary. The right subclavian is Blalock's artery of choice, though other surgeons prefer the left. Potts has shown that a direct anastomosis between the aorta and the left pulmonary artery is equally effective. A right sided aortic arch is present as an accompanying anomaly in about 20 per cent of tetralogy cases, and in these the left subclavian is usually readily available. On occasion other arteries may be used, and at times an end-to-end anastomosis may have to be resorted to, resulting in perfusion of one lung by the pulmonary and the other by a systemic artery.

At present it is difficult to deny the benefits of a shunting procedure to any patient suffering from tetralogy. These benefits often convert a cardiac invalid into a patient with only a mild handicap. Yet the result is far from a normal situation, and it remains to be determined how long the benefits will last. Patients with tetralogy and a compensating patent ductus arteriosus, which is the combination of anomalies that inspired the Blalock procedure, may ultimately develop increasing sclerosis of the pulmonary vessels which nullifies the benefits of the shunt and ultimately proves fatal. A direct attack upon the point of obstruction is a more physiologic approach. When this point is the pulmonary valve, a Brock procedure is therefore preferable, yet even under these circumstances, if there is much over-riding, the effect may be only to convert a tetralogy into an Eisenmenger's syndrome. A truly anatomical correction must await perfection of techniques which will allow operations to be carried out under direct vision within the cardiac chambers.

Transposition of the Great Vessels is the only other anomaly which has been treated surgically with any success. This condition is incompatible with postnatal life unless there is also another anomaly which permits mixing of the venous and arterial blood. Often in surviving infants this opening is in the auricular septum and in some instances it may be relatively small and ineffective. Blalock has reasoned that these patients should be helped by establishing a new and larger opening and has perfected a technique for accomplishing this by creating a window

between pulmonary vein and right auricle. He reports fair results in children but a high mortality in infants. This is a procedure admittedly still in the experimental stage and a problem fraught with many difficulties.

The challenge to perfect new methods to deal with the as yet uncorrectable anomalies is very great, for it has been proved that the heart of a child so afflicted can often be manipulated without disaster if certain essential requirements are met. Chief among these is an adequate continuous oxygen supply to the myocardium. The body must also receive a constant adequate circulation of oxygenated blood, and must at the same time rid itself of excess carbon dioxide. Thus skillful anesthesia is of utmost importance. It is known that healing of sutured blood vessels or myocardium is rapid and that new endothelium grows quickly over suture lines or grafts or non-irritating foreign material provided the flow of blood over them is smooth and swift. Hemorrhage can be successfully counterbalanced by adequate transfusion, if necessary given rapidly into peripheral arteries. But the circulation cannot be stopped even for a few minutes, and this fact at present limits intracardiac surgery to blind procedures carried out within the channels of the flowing blood stream.

This challenge has been accepted in numerous laboratories. Much work has been devoted to developing methods for temporarily carrying on circulation with mechanical devices outside the body with or without providing for gaseous exchange. Although it is possible to substitute a mechanical device for one side of the heart only, relying on the patient's own lungs for ventilation, such a device would have little usefulness in making possible operations to close openings between auricles or ventricles. The workers, especially Gibbon, who have succeeded in mechanically maintaining both circulation and respiration in animals are approaching a more practical solution. If this could be found, a new era of truly intracardiac surgery would begin, and many of the anomalies now beyond reach of the surgeon might come within his control. At present he can work only peripherally or blindly, but even within these limits he has added greatly to his understanding of the pathological physiology of the circulation, while at the same time restoring many patients heading for early death to comparative or complete health.

ENDOCRINE FACTORS IN HYPERTENSION*

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DURING the last few years, among other new developments in the hypertensive field, three topics have received an unusual amount of study and publicity, all related in some way to substances elaborated by endocrine structures. And so I plan to talk about the psyche, stress and steroids in relation to hypertensive vascular disease.

It is an accepted fact that emotional reactions may exert profound effects on the arterial pressure, particularly on the systolic level. These effects are brought about by increased cardiac action and vasomotor modification, largely as a result of the liberation of epinephrine. Not only can environmental factors, fear, excitement, and repressed as well as expressed emotions raise the blood pressure—in hypertensives even more than normotensives—but it can be said with equal authority that their relief or removal may reduce levels to an extent as dramatic as that produced by many of the more powerful drugs at our command. Without hesitation, one can state that psychological influences are of major importance and that application of this knowledge provides a means whereby many of the clinical manifestations of hypertensive vascular disease can be reversed readily. Our problem is to decide whether special etiological or therapeutic significance should be attached to these established facts.

There are two extreme attitudes taken by some individuals in the field. The first, championed primarily by psychiatrists, would have us believe that the entire sequence of events in essential hypertension is initiated by some antecedent emotional disturbance or characteristic personality pattern. The second, presented chiefly by internists, would attribute the whole process to an organic vascular disease, related perhaps

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to hereditary factors, but with no contribution from the psychological sphere. Some adherents of the former view have described a unique pattern, characterized by exaggerated dependent strivings, submissiveness coupled with stubbornness, suppression of hostility, and so forth. But here we step into a highly controversial field. The occasional reality of such patterns and the somewhat higher incidence of various forms of neurosis in association with hypertension cannot be denied. However, the number of patients studied is scarcely sufficient to lend statistical validity to such a correlation, and similar patterns have been portrayed in other conditions. Furthermore, it is difficult to avoid retrospective conclusions, to remain objective, and to obtain satisfactory control studies when dealing with the complexities of human nature in a complex disease state.

The position, that hypertensive disease has a psychosomatic component, now has some experimental support. Favoring the existence of neural and autonomic mechanisms, activated by emotional factors, is the observation that nor-epinephrine from the adrenal medulla is a pressor substance. Since some patients show a persistent residual hypertension even after the removal of a pheochromocytoma, Goldenberg and his associates[1] raise the question that frequent or prolonged secretion of adrenergic agents may set into action a self-perpetuating process. A new observation has been provided by Page and his colleagues[2] who recently reported that the brain, on appropriate stimulation, can elaborate a pressor material.

On the other hand, the hereditary nature of essential hypertension cannot be ignored and has been utilized as an argument against a strictly emotional basis for the disease. In addition, we have seen striking changes in emotional reactivity appearing coincidently with the onset of hypertensive disease even without the patient's knowledge of an elevated blood pressure. This "emotional decompensation" may be restored at times by sympathectomy. Intensive psychotherapy will lower the blood pressure in essential hypertension (as will rest, sedation and many other drugs and procedures); nevertheless, detailed study before and after such treatment has indicated lowering of pressure ceilings rather than of floors – but no established effect, to my knowledge, on the underlying disease or its rate of progression. Admittedly, these observations do not exclude the possibility of antecedent psychic trauma, or the added possibility that repeated emotional crises in a sensitized subject

result finally in an irreversible organic sequence. They do suggest, however, that no rigid position is tenable at the present time. Hypertensive vascular disease involves multiple considerations, and perhaps multiple components produce its final clinical and pathological picture. We have no right to dismiss any approach which might prove fruitful. This problem cannot be settled until it is approached with scientific methods, with the same appreciation of physiological variables, with the same critical evaluation and control studies as those employed in any other field of research effort. Only when these have been applied will we have the right to take a definite stand.

In modern medical parlance, the word "stress" has replaced "stimulus" and in the minds of some has become synonymous with the adrenal cortex. Selye[3] has defined it as "a condition, due to function or damage, which causes extensive regions of the body to deviate from their normal resting state." It could be suggested, however, that stress constitutes any change in the external or internal environment of sufficient magnitude to invoke a bodily alteration, i.e., flashing a light in the eye with resultant pupillary constriction. To Selye, after the major contributions of Claude Bernard and Walter Cannon, belongs the commendable credit for the more elaborate picture of the response to stress — the alarm reaction — but he would have us believe that nonspecific stress, through adrenal cortical participation, may produce hypertensive vascular disease and many other disorders from tonsillitis to adiposity.

Is stress important in the etiology of essential hypertension? Several investigators have confirmed the observation that pathological changes including an elevated blood pressure can be produced by appropriate stimuli. It must be kept in mind, however, that chronic elevations of blood pressure have been achieved only in the presence of added renal damage or in the course of the administration of excessive and unphysiological doses of endocrine preparations. Not only do pathological changes after stress require highly abnormal conditions, but they have been encountered in the exceptional animal, not as a rule; and control animals sometimes exhibit these same pathological changes.

The weight of evidence points toward the pituitary-adrenal axis only as an important adjunct to the response of tissues. An excess of adrenal cortical materials is not essential for the response to stress, inasmuch as patients with Addison's disease can develop hypertension, rheumatoid arthritis, nephrosclerosis and many other so-called diseases of adapta-

tion, and even adrenalectomized animals can be made hypertensive.[4] We have studied a patient with both hypertensive vascular disease and Addison's disease, who also had diabetes mellitus and rheumatoid arthritis.[5] On two separate occasions a high sodium chloride intake failed to modify the blood pressure. On the other hand, when maintained on constant small amounts of desoxycorticosterone daily, the blood pressure rose with an increased intake of salt and fell when the salt dosage was reduced. Certainly an excess of adrenal cortical hormones was not responsible for the restoration of the hypertension in this situation. As yet there is no evidence which establishes maladaptation to stress as a cause of disease. It remains merely an interesting and attractive bit of theoretical speculation.

Now let us turn to the endocrine structures themselves. Is there any evidence that their secretions, and particularly those of steroid composition, play a primary role in the etiology of essential hypertension? We need not consider the thyroid, parathyroids or gonads. Cushing's syndrome has been observed in several patients with carcinoma of the thymus, but this must be regarded as coincidence until proven otherwise. The literature abounds with references of hypertension in association with diabetes; but when clinical data are reviewed, documentation obtained, and postmortem material studied, one can establish that the incidence of true hypertensive disease is only slightly greater. The blood pressure changes among diabetics are due in large part to secondary arteriosclerotic complications. Although the posterior pituitary elaborates a pressor material, antidiuresis appears long before dosage is sufficient to modify blood pressure; the absence of fluid retention in hypertensive subjects leaves little need for consideration of this area. And finally, although hypophysectomy may have some effect on experimental hypertension, we have been unable to confirm the alleged relationship between acromegaly and hypertension and have found many instances of co-existent hypopituitarism and hypertensive disease.

Mention has been made already of the adrenal medulla and its nor-epinephrine, which can elevate the arterial tension through modification of peripheral resistance when administered in appropriate doses. An excess of circulating nor-epinephrine can be excluded as a cause for hypertensive vascular disease, both by direct analysis and the fact that the benzodioxane drugs fail to lower blood pressure in patients with this disorder. Nevertheless, the possibility must still be entertained that

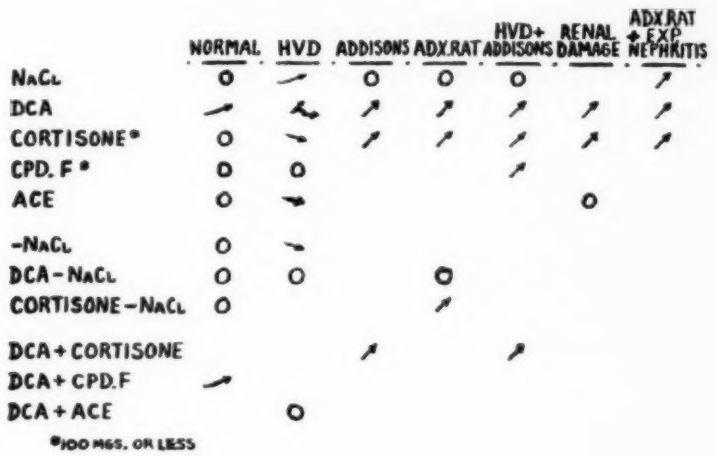

Figure 1

sensitization of blood vessels to normal amounts of nor-epinephrine could account for hypertension[1, 5, 6] and that we are not entitled as yet to eliminate the adrenal medulla from further consideration.

The adrenal cortex entered the hypertensive story in 1897 with the first description of pathological changes associated with certain adrenal tumors. Many additional evidences of a relationship have been provided since that time.[7] The hypertension of Cushing's syndrome, the hypotension of Addison's disease, and the frequent elevation of blood pressure in Addisonian patients treated with maintenance doses of desoxycorticosterone, are all well-documented and accepted observations. In addition, the adrenal cortex has been involved in experimental studies concerning the kidney-derived vasotropic principles, experimental renal hypertension, pressor amines, nor-epinephrine sensitivity, and many others. Furthermore, adrenal cortical changes have been described in animals on a reduced or excessive salt intake – of interest in connection with the effects of diet on blood pressure.

During the past eight years, together with Dr. Kermit Pines and others, we have pursued this problem through the technique of balance studies undertaken in a metabolic unit on patients with documented and usually uncomplicated hypertensive vascular disease. Some of our

results have been independently confirmed and extended along new lines by means of animal studies conducted by Drs. Knowlton, Seegal, Loeb and Stoerk. The combined results on steroidal modification of blood pressure are shown in Figure 1. It must be emphasized that this summary chart reflects certain dosages of steroid, under constant, quiet and controlled hospital conditions, and over certain specific periods of time. It might require modification if other conditions were employed. Presented in this form, however, it serves the purposes of this discussion.

It should be noted first that the addition or subtraction of dietary salt has a small but consistent effect on the blood pressure of uncomplicated hypertensives but is without effect in normotensives. Nor does an excessive salt intake influence the arterial tension in a hypertensive with adrenal cortical insufficiency unless small, daily injections of desoxycorticosterone are administered. These observations suggest that the sodium ion is related to blood pressure regulation, that the hypertensive handles salt or its restriction in a manner different from normal, and that an intact adrenal or some exogenous steroid is necessary for this action.

Desoxycorticosterone — but only in the presence of at least some dietary salt — raises the blood pressure under all of the circumstances tested, 40 mg. being no more effective than four. However, the pressor response is faster and greater in adrenalectomized animals, in Addisonian man, or in the face of renal damage than it is in normals, and dissimilar to the response in hypertensives. Patients with hypertensive disease, under these relatively basal conditions of study, invariably get an immediate small rise in arterial tension, but this is usually transitory over a period of a week or so. We recently had occasion to find this hypertensive pattern in a woman with a repeatedly normal blood pressure who only at a later date developed a persistent increase in pressure; in other words, an abnormal response to desoxycorticosterone may precede the onset of overt disease.[8] From this group of studies, the pressor properties of at least one steroid are confirmed, but again we find that the normal differs from the hypertensive.

Unlike desoxycorticosterone, at least in the adrenalectomized rat, little or no salt is required for the pressor effect of cortisone.[9] But similar to desoxycorticosterone, adrenalectomized animals, Addisonian patients, and subjects with renal damage of many varieties (with or without hypertension) show the most pronounced responses. Normals ex-

hibit little or no change with comparable dosage and duration of treatment, and uncomplicated hypertensives may even show a slight fall in blood pressure. The close structural similarity of Compound F (17-hydroxycorticosterone) to cortisone, its almost equal ability to produce hyperadrenalism and modification of rheumatic disorders, as well as our preliminary investigations of its action,[10] would lead us to suspect that its properties are similar. Thus we have other steroids which can be pressor under certain conditions, and once more an agent producing different effects under the influence of different disease states.

Is it conceivable that the adrenal cortex secretes some other substance capable of counteracting the effects of pressor hormones? This is suggested by the augmented action of cortisone in the adrenalectomized animal and in Addison's disease, by the studies employing adrenal cortical extracts in hypertensives and by the apparent blocking effects of such extracts when given simultaneously with desoxycorticosterone.[7] It is, however, far from established. Extracts contain many unknown ingredients. Furthermore, the interpretation of steroid action must be made with extreme caution. An administered agent may modify anterior pituitary secretions and alter the character of the existing adrenal hormones. Moreover, little is known concerning the pathways of degradation and the possible physiological actions of such by-products of metabolism.

Beyond doubt, the adrenal cortex plays a part in the regulation of blood pressure. Beyond doubt, the mechanisms involved are complex and not due to direct humoral action inasmuch as changes in arterial tension require days, not minutes, and are scarcely proportional to dosage. Could hypertensive vascular disease be the result of an over-production of some adrenal cortical hormone? Although the cortisone-like Compound F is now regarded as of definite adrenal origin, an excess gives rise to all the manifestations of hyperadrenocorticalism or Cushing's syndrome. These are not generally observed in essential hypertension. Only by postulating its conversion to another pressor agent, or by adding the concept of a simultaneous change in some other adrenal product, could such a theory be entertained at all. What about an excess of some desoxycorticosterone-like hormone, for desoxycorticosterone appears to be required for the maintenance of hypertension in the hypertensive Addisonian? Then one or two milligrams must represent an excess, for massive doses exert no greater effect. This could account for hyperten-

sion, and the diminished influence of this steroid in hypertensives might be interpreted as indicative of a state in which an excess is already present, but such a theory fails to explain the pressor action of cortisone. Nor can it be said with certainty that the adrenal cortex makes desoxycorticosterone. There is no definitive answer as yet; no proof of adrenocortical dysfunction in hypertensive disease has been provided by existing tests; and we must await the development of methods by which desoxycorticosterone-like compounds in the adrenal and circulation can be quantitated accurately.

Whether or not there is a possibility of hypertension of adrenal origin, it is clear that some types of hypertension can appear or be maintained in animals and in man in the absence of intact adrenals. Abnormal elevations of blood pressure have developed in Addisonian patients following renal damage by disease,[7] and bilaterally adrenalectomized rats become definitely hypertensive in response to cytotoxic serum nephritis providing a satisfactory nutritional state is maintained and a high sodium chloride intake employed.[4]

Despite the enthusiasm of recent years, it must be admitted that hormones function chiefly in an expediting capacity, as regulatory superstructures. They modify rather than initiate basic metabolic processes. Several recent developments of possibly great significance indicate that renal hypertension may represent the retention of a pressor substance which is normally excreted.[11, 12] Handler and Bernheim[12] have presented evidence that at least one form of renal hypertension, masked by dietary restriction, can be restored by appropriate adrenal hormonal therapy. Even if little else has been established, essential hypertension is undoubtedly a familial disease with an onset relatively early in life. If it should be proven that renal hypertension is the result of a failure to excrete rather than the excess production of a pressor substance, then it might be possible to integrate many isolated findings. For example, one might speculate that an unknown metabolite, acting on the arterioles or sensitizing them to some such substance as nor-epinephrine, is normally excreted and therefore present in too small concentration to do harm; that it is retained in renal disease; that it is produced in excess by an error of metabolism in essential hypertension; and that it is blocked at a renal or pre-renal level, or influenced in some way, when an excess of adrenal cortical hormones is present.

The tempo of research has increased immeasurably in recent years

and has emphasized among other things the role of psychological maladjustment and of stresses and strains of life in chronic and degenerative disease. The excitement of new developments, particularly in the realm of the synthesis of steroids, has opened entirely new fields of investigation and therapy. There is an important place for both the investigator in the laboratory or clinic, as well as the practitioner with his unique opportunities for direct contact with the patient, for close observation, and for critical evaluation of the responses to therapy. However, both must preserve their scientific critiques and not permit themselves to be swayed too far afield by attractive but unsubstantiated theories. For in the long run, only by careful fact-finding at a fundamental and then a clinical level, can we hope to find the solution to the many unanswered problems and help our patients who become ill.

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STATEMENT CONCERNING PROPOSED LEGISLATION ON SUPPLY OF ANIMALS FOR SCIENTIFIC RESEARCH*

The New York Academy of Medicine urges again that the New York State Legislature enact legislation at its 1952 session which will make available for medical research a small proportion of the stray dogs and cats now destroyed in animal pounds. In New York City about 70,000 dogs and a larger number of cats are put to death every year; in the whole state about 450,000 animals are disposed of annually.

The research that is carried on in hospitals, research institutes and other laboratories is indispensable for the development of drugs and procedures for the benefit of both human beings and animals. At present the investigators of disease in New York are handicapped in their endeavors because they are compelled to go into neighboring states to procure the 5,000 or 6,000 animals they require annually for experimental work. Even the State's own institutions, which now include two medical schools, and the City's Health Department laboratories are forced to undergo these inconveniences, at the same time that the City and State expend substantial sums to have thousands of animals destroyed. Thus important investigations are often delayed and money is wasted as a result of this inconsistency.

The State has already approved the use of animals in research by an amendment to Section 185 of the Penal Law adopted in 1947. The law now requires the State Health Department or its representative local agency, the City Health Department, to inspect for approval or disapproval all laboratories in institutions that require dogs and other animals for experimental research and medical education.

The bill proposed by the New York State Society for Medical Research contains additional safeguards to prevent cruelty to animals and also the accidental inclusion of a pet animal among those allocated for use in medical research.

First, the conditions for the approval of laboratories have been made more stringent. The rules governing approval include a requirement that animals shall be humanely treated, properly fed and housed, and that commensurate with experimental needs and with the physiologic function under study, all experiments involving pain shall be carried on under anesthesia.

Second, the time for which stray animals are to be held for possible redemption from the pound has been lengthened by three days.

Third, licensed animals surrendered to Humane Societies or to municipal authorities may not be released for research purposes without written consent of the owner.

Under these protective provisions there should be no possibility that a pet animal would be used for experimental purposes or that any animal so used would not be humanely handled.

In the interest of future progress in the prevention, diagnosis and treatment of disease, The New York Academy of Medicine wishes to impress upon the legislators and the public the urgent need for the allocation to scientific laboratories of a small number of animals from those now destroyed in the pounds.

October 24, 1951.

* Issued by the Committee on Public Health Relations.

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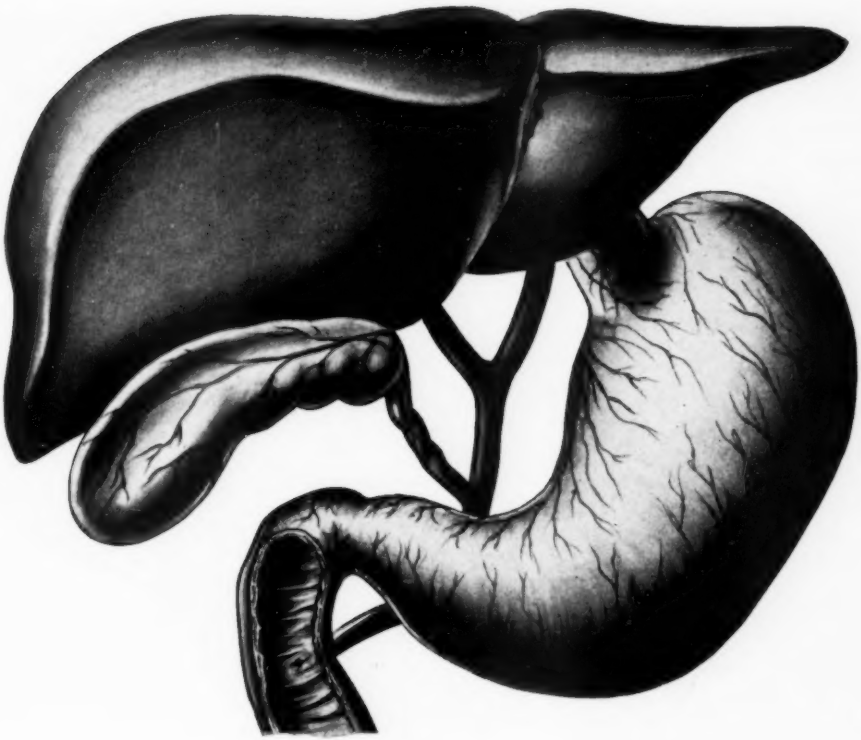

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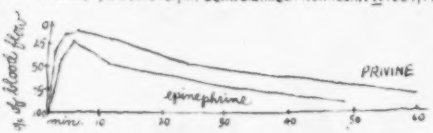

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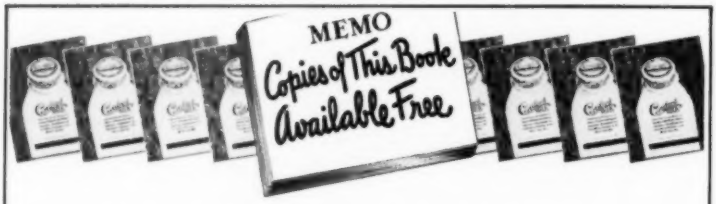

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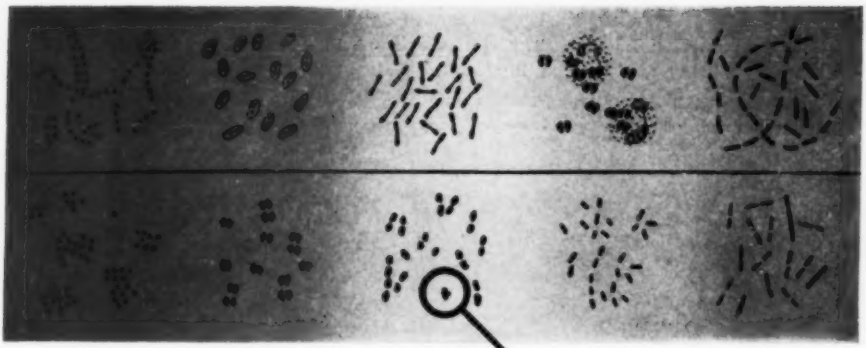

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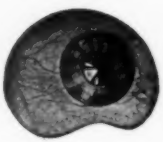

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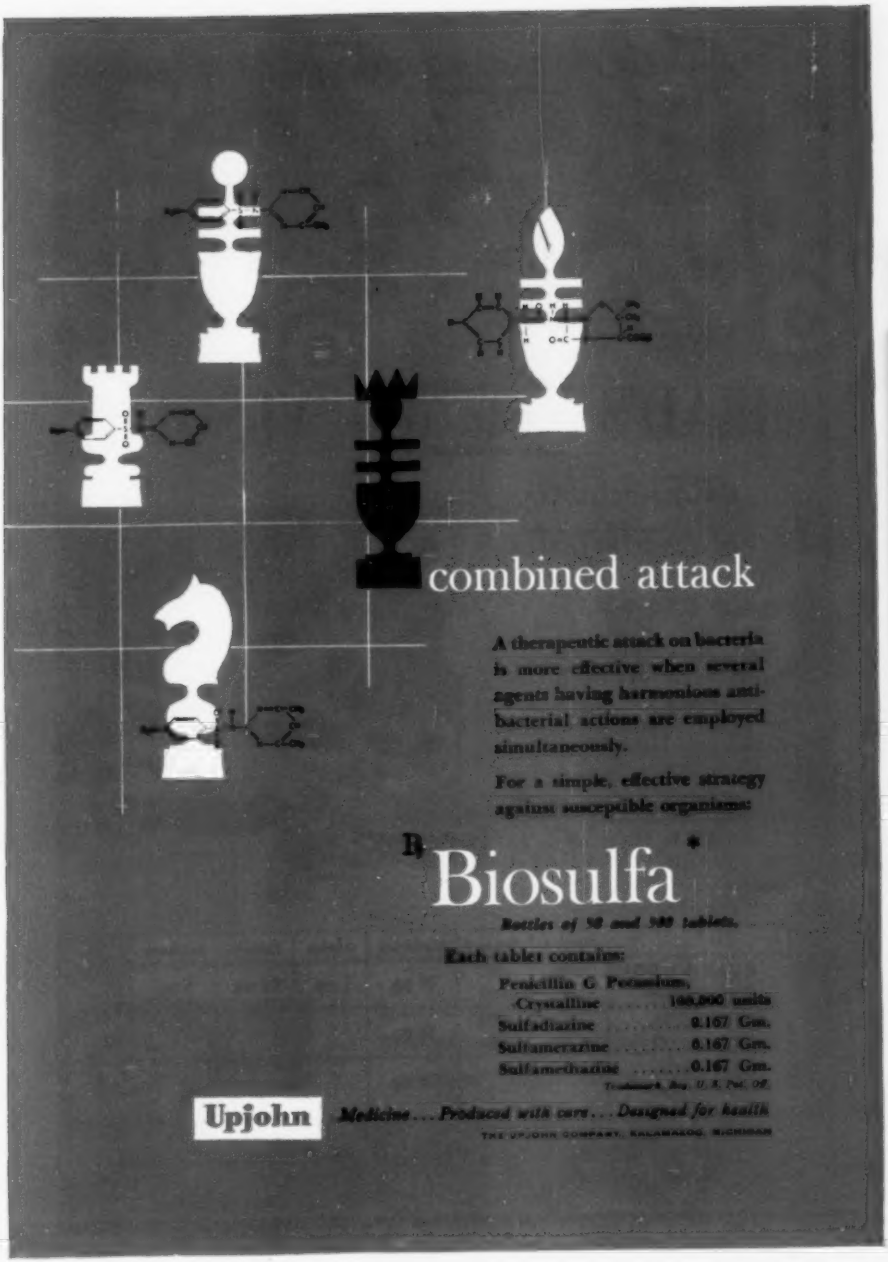
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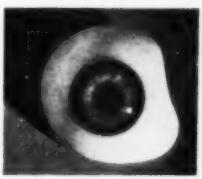

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Polymyxin B

parenterally
or
orally
or
topically. . . **according to the location of any condition due to:**

Pseudomonas aeruginosa (*B. pyocyaneus*), *Shigella*, and other gram-negative bacteria.

'AEROSPORIN' brand *Polymyxin B* (*Sulfate*) STERILE

500,000 Units
Equivalent to **50 mg.**
Polymyxin Standard

For intramuscular or intrathecal injection, to treat systemic or meningeal infections.

AVAILABLE TO HOSPITALS ONLY

'AEROSPORIN' brand *Polymyxin B* (*Sulfate*) STERILE

200,000 Units
Equivalent to **20 mg.**
Polymyxin Standard
For topical use only

For preparing solutions and ointments (0.1% to 0.25%) for topical use.

AVAILABLE TO HOSPITALS AND RETAIL PHARMACIES

'AEROSPORIN' brand *Polymyxin B* (*Sulfate*) COMPRESSED

500,000 Units
Equivalent to **50 mg.**
Polymyxin Standard

For oral use in enteric infections only.

AVAILABLE TO HOSPITALS AND RETAIL PHARMACIES

BURROUGHS WELLCOME & CO. (U.S.A.) INC., *Tuckahoe 7, N. Y.*

DAY

Each Dainite Day Tablet contains:

Sodium Pentobarbital	¼ gr.
Aminophylline	3 gr.
Ephedrine HCl	¼ gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

NITE

Each Dainite Nite Tablet contains:

Phenobarbital	⅜ gr.
Sodium Pentobarbital	½ gr.
Aminophylline	4 gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

Dainite Tablets provide day and night protection for the asthmatic patient, with almost complete absence of side-effects.[1] In a series of 100 patients with bronchial asthma and pulmonary emphysema receiving Dainite Tablets on arising and retiring, only 2 patients noted nausea[1] despite the daily, full therapeutic dose of aminophylline. Marked objective improvement of respiratory function, with significant relief of wheezing, dyspnea and cough, has been observed.[1]

DAINITE (Irwin-Neisler) provides a night and day difference in treatment that meets the requirements of the active and the resting patient. The use of antinausea factors safely permits a more effective, prolonged dosage of aminophylline than previously available in asthmatic preparations.

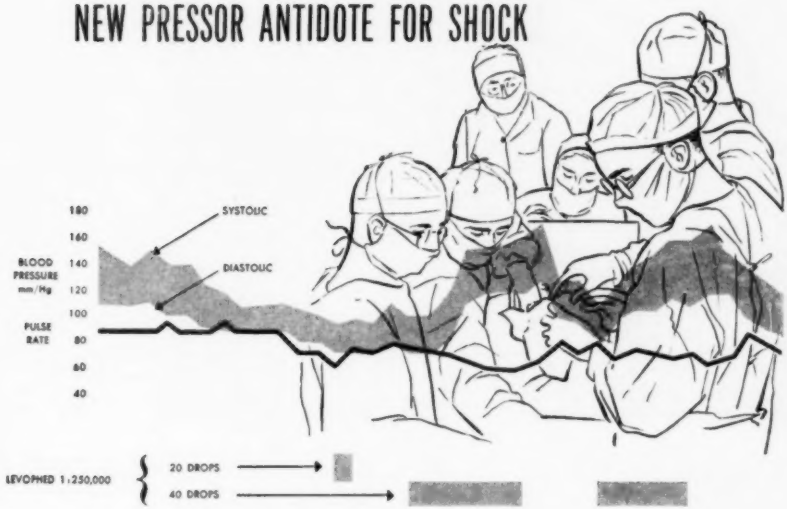
Supplied as the DAINITE UNIT containing 48 Day Tablets and 18 Nite Tablets in a unique dispensing unit . . . at prescription pharmacies everywhere. **Average Dose:** One Dainite (Day) Tablet t.i.d. before meals; one Dainite (Nite) Tablet at 10 P.M.

1. J.A.M.A. 147:730-737 (Oct. 20) 1951. Literature and detailed dosage information on request.

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Research to Serve Your Practice

NEW PRESSOR ANTIDOTE FOR SHOCK



LEVOPHED®

LEVO-ARTERENOL

THE TRUE VASOCONSTRICTOR HORMONE OF THE ADRENAL MEDULLA

Levophed "acting through peripheral vasoconstriction, has proved to be our most powerful stimulant to blood pressure."[1]

It "was possible in every case to achieve and to maintain a satisfactory blood pressure during operation . . . No supplementary vasopressors were required when arterenol was given intravenously."[2]

- IMMEDIATE EFFECT
- SHORT DURATION OF ACTION
- LOW TOXICITY
- ABSENCE OF CORONARY CONSTRICTION

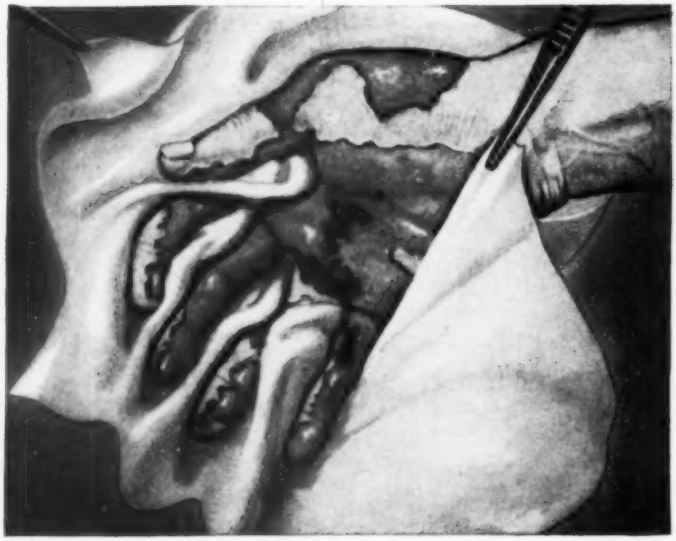
SUPPLIED: Levophed solution 1:1000 in ampuls of 4 cc (must be diluted in 1000 cc. of infusion fluid), boxes of 10.

Winthrop-Stearns INC.
New York 18, N. Y. Windsor, Ont.

WRITE FOR DETAILED INFORMATION.

1. Phillips, O.C., and Nicholson, M. J. Surg. Clin. North Am., 30:705, June, 1950.
2. Wilson, C.M., and Bassett, R.C. Univ. Michigan Med. Bull., 16:57, March, 1950.

Levophed, trademark reg. U. S. & Canada



new!

Davis & Geck Aureomycin DRESSING

An important advance in wound therapy

Aureomycin Dressing is an entirely new non-adherent dressing with antibiotic action having the following advantages:

1. *Broad-spectrum.* It concentrates locally the antibiotic now recognized as the most versatile yet discovered with a wider range of activity against both Gram-positive and Gram-negative micro-organisms than any other remedy.
2. *Prevents infection.* It suppresses growth of many organisms which might be present in the wound or later contaminate it.
3. *Non-adherent and non-macerating.* Minimizes abrasion of healing wounds and avoids trapping of moisture conducive to bacterial growth.
4. *Promotes healing.* When infection is controlled healing takes place faster.
5. *Non-toxic.* Reactions to Aureomycin Dressing so far have not been observed.

also new Aureomycin **PACKING**

For use wherever plain or chemically impregnated packing was formerly used.

Available through D&G's surgical supply dealers

Davis & Geck, Inc.

A unit of American Cyanamid Company

57 Willoughby Street, Brooklyn 1, N. Y.

Surgeons agree on D&G

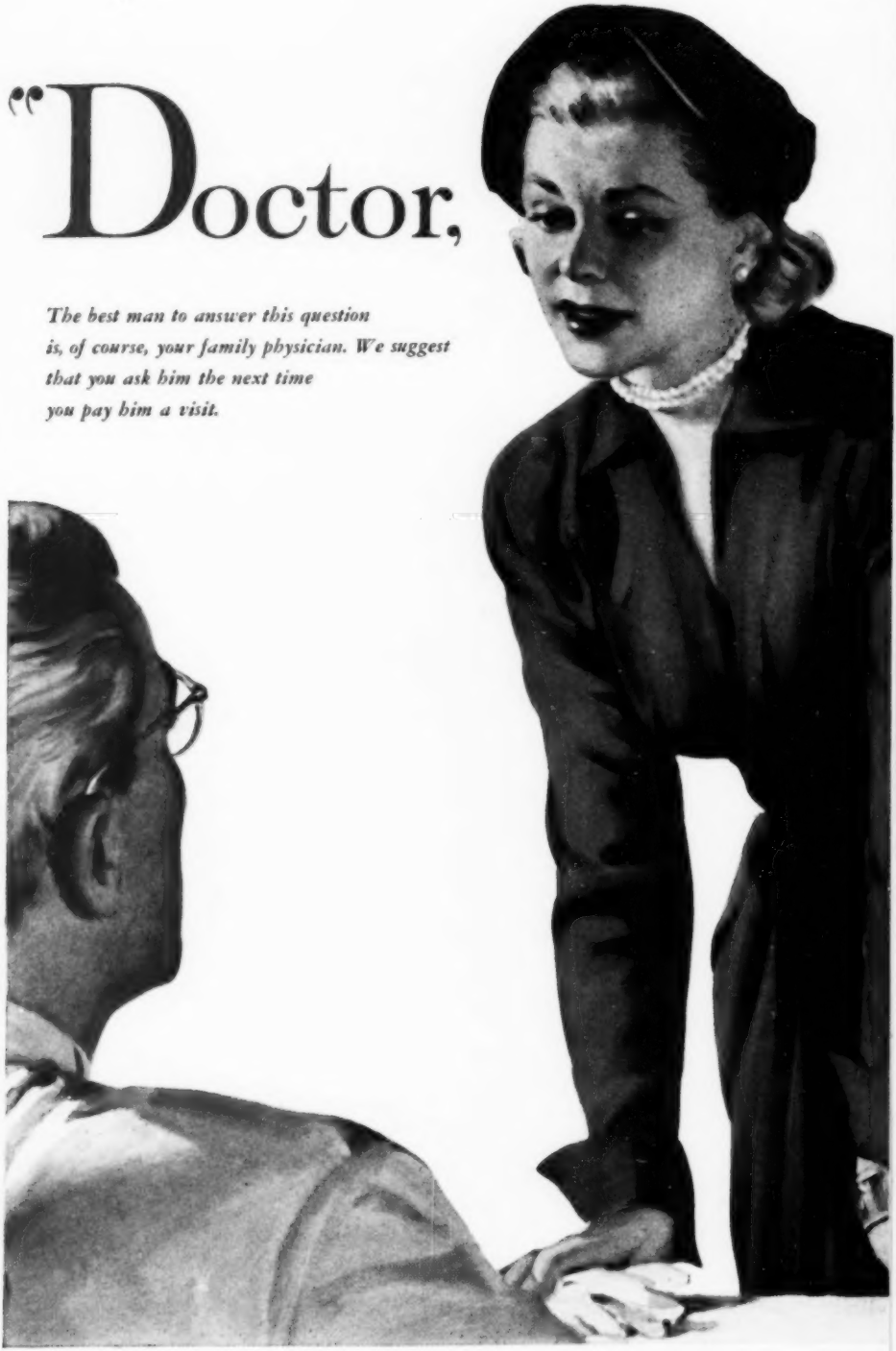
Description:

Aureomycin Dressing **is an 8" x 12" gauze dressing of close mesh impregnated with 16 Gms. of 2% aureomycin hydrochloride ointment.**

Aureomycin Packing **is double selvage-edge gauze, in ½" x 24", 1" x 36" and 2" x 36" strips.**

"Doctor,

The best man to answer this question is, of course, your family physician. We suggest that you ask him the next time you pay him a visit.



I'd like to know...

what is a NUTRITIONAL TIME BOMB?"

"Nutritional Time Bomb" is science's dramatic name for an equally dramatic discovery about diet . . . the discovery that injuries caused by mistakes in diet may not reveal themselves until years later.

Like actual time bombs, these injuries remain hidden and unrecognized, exploding into symptoms when it is too late to do anything about them. Thus, the dietary wrongs of childhood may be visited upon the adult.

Such scourges of later life as tooth decay, goiter, high blood pressure, heart disease, anemia and hardening of the arteries are not necessarily caused by present diet faults. They may be the delayed effects of earlier injury, where a dietary deficiency has existed too long.

A sound child body—the foundation of a sound adult body—must be built from the food that goes into it. The true effect of a mother's care during childhood has only begun to be understood. And, since eating habits are formed in childhood, the conscientious parent can do much to insure the child against later penalties of wrong eating.

The protective foods should be used generously in the daily diet. Important among these are bananas—long prescribed by doctors as one of the first solid foods for infants. Bananas have a well-rounded supply of vitamins and minerals, and are distinctly beneficent in their action upon the digestive tract. Because of the many appetizing ways in which bananas can be served, as well as because of their nutritional value, they are now being more widely used than ever.

FOR HEALTH, EAT AND ENJOY A PLENTIFUL VARIETY OF THE "RIGHT" FOODS

UNITED FRUIT COMPANY

NOW

palatable
penicillin therapy
with

concentrated convenience for infants

Pen-Drops*

100,000 units Potassium Penicillin G per cc.

highly concentrated oral penicillin liquid
bottles of 10 cc.

elixir-ease for children and adults

Liquapen*

250,000 units Potassium Penicillin G per teaspoonful (5 cc.)

effective dosage: 2 teaspoonfuls
3 or 4 times daily—permits normal eating and sleeping schedules

bottles of 50 cc.

readily accepted by all patients—avoids the discomforts of parenteral therapy

*Trademark

Antibiotic Division Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*